

COURSE AND PROGNOSIS IN CAROTID DISEASE

Non-invasive studies in patients with
carotid stenosis and occlusion

Bo Norrving

LUND 1981

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AKADEMISK AVHANDLING

Som med vederbörligt tillstånd av Medicinska Fakulteten
vid Universitetet i Lund för vinnande av medicine dok-
torsexamen kommer att offentligen försvaras i Föreläs-
ningssal 2, Centralblocket, Lasarettet i Lund, fredagen
den 11 september 1981, kl 09.15

av

BO NORRVING

leg läk

Vg

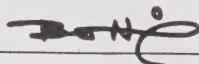
Organization LUND UNIVERSITY		Document name DOCTORAL DISSERTATION	
Department of Neurology		Date of issue 1981-09-11	
		CODEN: LUMEDW/CMENL-1002/1-47/1981	
Author(s) Bo Norrving		Sponsoring organization	
Title and subtitle COURSE AND PROGNOSIS IN CAROTID DISEASE. Non-invasive studies in patients with carotid stenosis and occlusion.			
Abstract 1 With non-invasive direct Doppler examination of the carotid bifurcation, the lower limit for detection of a stenosis is close to 50 % (lumen diameter reduction). Sensitivity for stenoses ≥ 50 % or occlusions was 98.3 % and specificity for stenoses < 50 % or normal vessels was 96.6 %. 2 After unilateral carotid endarterectomy a considerable but mostly clinically silent progression of carotid lesions occurs both in the operated and non-operated carotid arteries. In 64 patients with unilateral carotid surgery, Doppler examination at follow up (mean 6 years after surgery) revealed a recurrent stenosis (≥ 50%) or occlusion in 37 % of the operated vessels, a progression rate not significantly different from that found in the non-operated carotid artery (27 %). Almost one-third of the progressive lesions were associated with symptoms of TIA or stroke, as opposed to only 5.5 % of vessels without progression of lesions ($p < 0.001$). 3 In 50 surviving patients with carotid occlusion followed for a mean of four years, a low annual incidence of further stroke ($\sim 1\%$) and TIA ($\sim 1\%$) on the occluded side was found. Anticoagulant treatment in 40 % of the patients may have contributed to the low recurrence rate. 4 The acute outcome in carotid occlusion is closely related to the type of collateral flow. The anterior circle of Willis was found to be the most important collateral pathway, superior in capacity to the ophthalmic artery. The collateral capacity via the circle of Willis is mirrored by the ophthalmic flow pattern. In some patients a severe stroke may be caused by massive embolism or propagation of the thrombus beyond the circle of Willis. 5 rCBF measurement by the non-invasive ¹³³Xenon inhalation technique in 39 patients with subacute-chronic unilateral carotid occlusion revealed as an almost constant finding an interhemispheric asymmetry, which was related to the severity of the cerebral lesion and not to the type of collateral flow. An ischemic focus was rarely identified with the technique used. The CBF response to induced hypercapnia seems to be the variable most closely reflecting the collateral hemodynamic features in carotid occlusion. An impaired CO₂ response was found in patients with retrograde ophthalmic flow and in patients with circle of Willis flow associated with a contralateral carotid artery stenosis ≥ 50 per cent.			
Key words Carotid stenosis, carotid occlusion, TIA, stroke, carotid endarterectomy, extra-intracranial bypass surgery, Doppler ultrasound, rCBF measurement, angiography.			
Classification system and/or index terms (if any)			
Supplementary bibliographical information		Language English	
ISSN and key title		ISBN	
Recipient's notes	Number of pages 119	Price	
	Security classification		

DISTRIBUTION BY (NAME AND ADDRESS)

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Printed in Sweden by
Info-tryck, Malmö 1981



The importance of a blood supply to the brain was known by the Greeks. They named the great arteries of the neck carotid (Gk. karotein = to stupefy) because of the observation that sustained pressure of these vessels caused anesthesia sufficient to allow ritual circumcision. The sculpture above is from the Parthenon (447-432 B.C.) and shows a carotid compression, causing adverse seizure to the right.

The present thesis is based on the following papers, referenced in the text by Roman numerals:

- I Norrving B and Cronqvist S (1981): DOPPLER EXAMINATION OF THE CAROTID ARTERIES. A comparative study with angiography. Acta Neurol Scand, in press.
- II Norrving B, Nilsson B and Olsson J-E: CAROTID DISEASE PROGRESSION AFTER ENDARTERECTOMY: A Doppler ultrasound study. Submitted to Annals of Neurology.
- III Norrving B and Nilsson B (1981): CAROTID ARTERY OCCLUSION: Acute symptoms and long term prognosis. Neurological Research, in press.
- IV Norrving B, Nilsson B and Cronqvist S (1981): CEREBRAL ISCHEMIC SYMPTOMS IN CAROTID ARTERY OCCLUSION: Role of hemodynamic factors. Neurological Research, in press.
- V Norrving B, Nilsson B and Risberg J: rCBF IN PATIENTS WITH CAROTID OCCLUSION: Resting and hypercapnic flow related to collateral pattern. Submitted to Stroke.

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INTRODUCTION

Despite important advances that have been made, cerebrovascular disease remains a major public health problem, and its conquest continues to challenge clinicians, clinical investigators and laboratory scientists with a breadth of interests, applying a variety of methods. For the individual, stroke commonly is the most devastating manifestation of atherosclerosis, because it may rob the victims of their independence, physical prowess, dignity and ability to communicate. For the community the economic burden imposed by stroke is heavy. Stroke constitutes the third most common cause of death, is a main cause of handicap and requires more days to be spent in hospital wards than any other somatic disease.

Cerebrovascular disorders may be divided into hemorrhagic and ischemic. Cerebral hemorrhage, closely associated with hypertension, is caused by rupture of a vessel affected by degenerative wall changes or microaneurysm. Cerebral ischemia, caused by thrombosis or embolism, is by quantity the most important clinical problem, being responsible for about 80 per cent or more of all cases with stroke (Mohr et al 1978). By far, the most common underlying pathogenetic factor in ischemic symptoms is arterial disease within the carotid artery, many aspects of which have been gained during the last decades. More recently, the introduction of new modes of therapy has focused interest upon some aspects on which previous information is incomplete. Other aspects of carotid arterial disease have only recently been available to study, due to the introduction of non-invasive techniques to detect carotid lesions and non-invasive methods to measure the cerebral blood flow (CBF).

In the Clinical background the evolution of research and current concepts on carotid arterial disease will be outlined, followed by a description of the development and application of non-invasive methods to detect carotid stenosis or occlusion and to measure the CBF.

Clinical background

Early in this century pathological studies established the importance of extracranial occlusive disease of the internal carotid artery and its relationship to cerebral infarction. Chiari (1905) discussed the association of carotid bifurcation atheroma with emboli in the intracranial branches of a vessel causing a stroke. He pointed out that the main source of emboli in the older age was mural thrombi of the carotid bifurcation. J Ramsey Hunt (1914) examined the carotid pulsation in 20 cases with hemiplegia, finding it absent on the appropriate side in four instances. However, in those years thrombosis of the internal carotid artery was commonly thought to be less important than thrombi of the intracranial vessels. There was good reason for this view since it was known that surgical ligation of the internal carotid artery in the neck was not usually followed by brain damage, a fact used by Thomas Willis to deduce the function of the circular anastomose at the base of the brain. It was recognized that clinical diagnosis in separating extracranial and intracranial disease lacked precision, but as the only check upon diagnosis was the autopsy, there was little possibility of progress. One of the most important autopsy studies was Hultquists extensive report on carotid occlusion (1942). He found a carotid occlusion in 2.9 per cent of 1300 unselected autopsies.

The concept of carotid disease was slow to gain acceptance and in the early 1950s, Fisher again had to stress the high frequency of lesions in the carotid artery as a cause of cerebrovascular symptoms (Fisher 1951, 1954). In the classical paper of 1951, Fisher emphasized the role of TIAs as a sign of impending stroke and pointed out embolism and hemodynamic factors as possible pathophysiological mechanisms.

The introduction of angiography by Egaz Moniz (1927) represented a major advance in the study of cerebrovascular disease. Sjöqvist (1936) reported the earliest angiographic diagnosis of carotid occlusion, and one year later Moniz et al (1937) described four patients with carotid occlusive disease. However, these cases were exceptional. During the early phase angiographies were performed mainly in patients with intracranial aneurysms and mass lesions. Not until the early 1950s was angiography more generally performed in patients with cerebrovascular disease. At that time angiographic techniques were improved, but the main stimulus was the introduction of specific medical and surgical therapy.

Although anticipated by Fisher (1951), it was the report by Millikan and associates (1955) at the Mayo Clinic that initiated the broad use of anticoagulant therapy as a prophylaxis for cerebral infarction in patients

with TIA. Since that time this issue has been the subject of many reports. Nevertheless, the definitive place of anticoagulant therapy has not been firmly established. As pointed out by Brust (1977), no study has been carried out with modern design and execution and with a sufficient number of patients followed long enough to allow firm conclusions. Although there is a strong clinical body of evidence on the value of anticoagulant therapy on an empirical basis, its benefit has not been unequivocally established in any study. Today, any modern trial faces the problem of obtaining a representative, non-historical control group against which any therapeutical claims might be assessed. Because the attention to medical risk factors has increased considerably during the last years, it is possible that the natural prognosis of TIA has been markedly altered, since e.g. the study by Whisnant et al (1973).

Specific surgical therapy by carotid bifurcation endarterectomy was first reported by Eastcott et al (1954), although the first operation had been performed one year previously by deBakey (deBakey 1975). During the early phase the rational application of carotid endarterectomy was hampered by limited knowledge on the pathophysiology of stroke and the hemodynamics of carotid stenoses. It was generally assumed that most carotid stenoses reduced blood flow to the point at which infarction occurred. Carotid surgery for acute thrombotic stroke was at that time adopted, based on the assumption that the stroke deficit would be alleviated by the operation. However, Wylie and colleagues (1964) found that in patients with dense ischemic stroke, restoration of the carotid blood flow could lead to fatal edema or hemorrhage into the infarct in as much as 50 per cent of cases. This, in addition to two other findings, marked a turning point. Studies by May et al (1963) and Brice et al (1964) established that a carotid stenosis is of hemodynamic significance, i.e. reduces the blood flow, only when the cross-sectional area is reduced to about 80 per cent or more, corresponding to a residual lumen diameter of less than 1.5-2.0 mm. At about the same time, findings of retinal microemboli in patients with amaurosis fugax provided an explanation for TIA, which previously had been the basis of considerable argument as to its pathogenesis. Fisher (1959) and Ross Russel (1961) observed patients during transient attacks of monocular blindness. They saw small, white or yellow bodies passing along the retinal arteries, impacting for a time on bifurcations and finally fragment and move peripherally. Subsequent studies revealed that the bodies consisted of aggregations of platelets or atheromatous debris/cholesterol esters (Hollenhorst 1960, Mc Brien et al 1963). Since there was no reason to believe that the retinal arteries would have

monopoly of these emboli, the microembolic theory for TIAs in general gained wide acceptance. Although numerous other causes of TIA have been identified later, artery-to-artery microembolism still holds as the most important pathophysiological mechanism (Barnett 1979). As a consequence, carotid endarterectomy has been applied mainly on a prophylactic basis to remove a potential source of emboli.

As with anticoagulant therapy, numerous studies have been performed to elucidate the possible benefit of carotid endarterectomy (for review see Millikan 1980). The most extensive trial, the Joint Study of Extracranial Arterial Occlusion led by W.S. Fields, collected data on more than 4000 stroke patients, only part of whom were reported. No statistically significant benefit was demonstrated for any of the subgroups in that study when perioperative complication rates were included in the results (Fields et al 1970). In the subgroup with unilateral carotid stenosis there was a trend toward benefit from surgery.

A number of criticisms have been made of the Joint Study, some of which also apply to other surgical studies. The non-surgical group received a variety of medical treatments, including anticoagulants, not specifically stated. There was a marked difference in the mortality and morbidity of the surgical procedure between various centers, and also during the course of the study. Because the complication rate is influenced by the severity of the operated lesion, extent of multivessel involvement and medical risk factors, e.g. coronary disease (Sundt et al 1975), comparison of the results from different surgical studies is complex. Also, very little is known about the relationship between the severity and type of a carotid lesion and the future risk for stroke, although conceivably this factor is of prime importance in evaluating any clinical trial. Apart from randomization for various risk factors, also the non-surgical and surgical groups should be comparable as to the extent of the arterial disease. This is a most difficult task, especially so since angiography is a prerequisite for surgical treatment but not for medical. Although most physicians consider carotid endarterectomy a reasonable procedure in patients with unilateral carotid stenosis appropriate to the side of the symptoms (provided that surgery can be carried out with a low complication risk), after 25 years experience the actual benefit of carotid surgery has not been definitively accredited. Also, largely unsettled is the long term patency of the operated vessels. Whereas the incidence of symptomatic recurrent stenosis is considered to be low (Callow 1980), it is clear that this figure does not equal the asymptomatic recurrence rate.

Angiographic studies of patients with TIA and stroke have shown that about one-third of the arterial lesions are not amenable to standard carotid surgery in the neck (Hass et al 1968, Marshall 1971). These lesions include internal carotid occlusion, inaccessible carotid stenosis (high cervical or intracranial), middle cerebral artery stenosis and occlusion. Of these, internal carotid artery occlusion is the single most common entity. With the introduction of extracranial-intracranial bypass surgery, by which the superficial temporal artery is anastomosed to a cortical branch of the middle cerebral artery, surgical therapy for these lesions became available. The first operation was performed in 1967 by Yasargil (Yasargil 1969), and subsequently bypass surgery has been applied in a large number of patients. The surgical technique has been advanced so that, in trained hands, the procedure can be carried out with a low morbidity and mortality rate, and with a high patency rate of the anastomosis (Sundt et al 1976).

Despite the technical success and theoretical attraction of bypass surgery, its definitive value at present remains unproven, because the natural long term prognosis and pathophysiological mechanisms in specific lesions are not adequately known. Any therapeutical claims have to be judged against the expected prognosis in each separate group of arterial lesion that may be considered for surgery. The pathophysiological mechanisms are often complex and different for each lesion. Embolic and hemodynamic factors may operate alone or in combination in producing the initial symptoms and later ischemic events. The pathogenesis of new events may include situations that would benefit more from medical or other surgical measures than from bypass operation. Because bypass surgery is hemodynamically directed the role of each pathogenetic factor must be evaluated separately.

A Cooperative randomized study to determine the prophylactic value of bypass surgery was initiated in 1977, and is at this writing in progress (Barnett & McCormick 1980). Criteria for entry are TIA or minor stroke associated with otherwise surgically inaccessible carotid or middle cerebral arterial lesion. No detailed hemodynamic considerations are included.

Although bypass surgery is most commonly applied with the aim to reduce the incidence of further TIA and stroke, a "therapeutic" approach, i.e. to reduce the severity of a stroke deficit, has also been adopted (Spetzler 1979). However, the variability in spontaneous stroke recovery makes it exceedingly difficult to convincingly attribute any clinical improvement to the surgical procedure itself, and present evidence remains anecdotal.

The last decade has been marked by an increased understanding of the important role of platelets in initiating arterial thrombosis (for review

see Fuster & Chesebro 1981). When the endothelial barrier is disrupted, platelets are exposed to collagen which induces reactions of platelets with the vessel wall (adhesion) and with each other (aggregation), independent of the coagulation system. These reactions are in large part consequent upon local prostaglandin concentration and type. Attention has been focused on prostaglandins of high biological potency, which have very short half-life in plasma. Thromboxane A_2 , present in platelets, induces platelet aggregation whereas prostacyclin (PGI_2), produced in the vessel wall, is a powerful inhibitor of platelet aggregation. After the identification of drugs, e.g. aspirin, dipyridamole and sulfinpyrazone, that alter platelet function at various steps, these farmaceuticals (mainly aspirin) have been widely used as an alternative to anticoagulant treatment in patients with TIA and minor stroke. Compared to anticoagulant therapy, anti-platelet treatment does not necessitate laboratory monitoring of treatment effect and induces a lower risk for serious hemorrhagic side effects, mainly intracerebral hematoma.

Two major collaborative trials have been conducted to study the usefulness of anti-platelet therapy in cerebral ischemic attacks. The Canadian study (Canadian Cooperative Study Group 1978) suggested that aspirin was of benefit in males, whereas in the U S study (Fields et al 1977) treatment effect was primarily seen in patients with multiple TIAs and an appropriate lesion. However, the design, conduct and statistical analysis in these studies have been the subject of considerable discussion and disagreement as to the interpretation of the results. In both studies, the use of a combination of, rather than single, end-points to obtain statistical significance is doubtful practice. If death is included as an end-point, the results are weighted for heart disease. Among patients with TIA, only about 25 per cent of deaths are due to stroke, nearly 50 per cent are due to heart disease and 25 per cent to other conditions (Cartlidge et al 1977). More appropriate is to assess the effect of therapy on stroke occurrence exclusive of other conditions. Also, the aspirin dosage used in both studies has been questioned. A low aspirin dose may be sufficient to inhibit production of thromboxane A_2 , whereas an excessive dose of aspirin may be unfavourable because also the production of the antiaggregating prostacyclin by the vessel wall is inhibited (O'Grady & Moncada 1978). At present, consensus is that aspirin continues to share with anticoagulant and surgical therapy an equivocal role in the prevention of stroke.

A major limitation of joint clinical trials on anti-platelet or anticoagulant therapy is that patients with widely different arterial lesions

and probably also different causes of the symptoms are evaluated as a homogeneous group. The natural course, and also the rational therapeutic approach, may be considerably different in various subsets of patients. Even if artery-to-artery embolism is the main pathophysiological mechanism when a carotid lesion is present, local alterations in blood flow in the stenotic region may be different. Retarded blood flow, which may be identified in the region of a moderate or severe stenosis (Reneman & Spencer 1979), facilitate the thrombotic process once it is initiated and may prevent the dilution of coagulant factors to subcritical concentrations. In these patients anticoagulants (or surgery) may seem to be a more rational treatment than anti-platelet therapy. Also, it is recognized that in a proportion of patients angiography will not reveal any vascular pathology, even if the examination is performed shortly after the ictus. A lacunar infarction, caused by degenerative lesions in intracerebral arterioli, may be preceded by TIAs which are clinically indistinguishable from TIAs of other origin (Fisher 1965). Clearly, further research is needed to determine the most rational therapy in specific patient groups.

As evident from these remarks, the complexity and pathophysiological diversity of carotid arterial disease have been main obstacles in unequivocally documenting the benefit of any of the various treatments presently available. The difficulties encountered in selecting the optimal therapy on an individual patient basis are indeed considerable, and opinions differ sharply on the management of carotid arterial disease, whether symptomatic or not. Although an immense amount of data have been accumulated on carotid disease, several major problems remain unresolved.

Non-invasive diagnosis of carotid stenosis and occlusion

The use of angiography in stroke patients has been restricted mainly to patients considered for carotid endarterectomy. Apart from economical reasons, the small, but definitive, risk of angiography has prevented its application to other aspects of carotid arterial disease on which information presently is incomplete. These include the incidence of arterial lesions in various populations with and without cerebral ischemic symptoms and the sequential evolution of such lesions. Also, in the clinical setting the indication for angiography may be debated in some groups of patients, such as those presenting with symptoms and signs that are only equivocal for carotid arterial disease or patients who present with carotid symptoms but have relative contraindications for surgery. These different situations are suitable application areas for non-invasive techniques to detect carotid

lesions.

The main development of these techniques has taken place during the last 10-20 years. A large number of techniques, based on different physical principles, and monitoring the anatomy or different physiological properties of the carotid circulation, have been introduced. Because most tests in current use are based on Doppler ultrasound, the fundamentals of this technique, also used in the present study, will be described in more detail. Thereafter, the relative merits and possible clinical usefulness of different non-invasive tests will be outlined.

Doppler ultrasound: physical background

The Doppler principle is named after Christian Doppler, professor of physics in Wien, who in 1842 deduced that the movement of stars towards or away from an observer caused a frequency shift of the emitted light waves. It was soon recognized that the same principle concerned also sound waves emitted from a moving subject. However, Doppler technique as a practical tool was not introduced until 1959, when Satomura (1959) showed that the acoustic energy back-scattered from moving cells in a blood vessel was Doppler frequency shifted, and described the first Doppler ultrasound equipment. The transcutaneous version of this instrument was introduced by Franklin et al (1961) and it now became possible to measure blood flow velocities by a non-obtrusive method. A direction sensitive equipment was described by McCloud (1967).

In Doppler flow-meters a beam of ultrasound waves (at the MHz level), emitted from a piezoelectric crystal mounted at the end of a probe, is transmitted diagonally through the vessel wall into the blood stream. Ultrasound, back-scattered from particles in the flowing blood, mainly the red cells, is received by a second crystal mounted on the same probe. The frequency shift (the Doppler signal; f_d), which is retrieved by mixing the transmitted and received signals, is in the audio range and equals:

$$f_d = \frac{2 f_t v \cos \alpha}{c} \quad c \gg v \quad (1)$$

in which f_t = transmitted frequency, v = velocity of the particles, α = the angle between the transmitted sound beam and the direction of the velocity of the particles and c = the velocity of the sound in the medium.

In Doppler flow-meters ultrasound can be transmitted continuously (continuous-wave, CW, Doppler) or intermittently (pulsed Doppler). In the continuous-wave Doppler, the Doppler signal from a single vessel is a mixture of signals of different velocities that exist within the vessel. In

pulsed Doppler flow-meters ultrasound is emitted in short bursts, rather than transmitted continuously. Usually, the same piezoelectric chrystal operates both as transmitter and receiver. By varying the delay between transmission and reciver-mixing the blood velocity within a small volume (the sampling volume) of the vessel can be determined. The simultaneous use of several pulsed Doppler transducers (multichannel flow detector) makes it possible to determine the flow velocity profile within the vessel.

The development of pulsed Doppler equipments has been slow, mainly because of its complexity and expensiveness. Transducer construction is more complicated in pulsed than in CW devices. To obtain sharp pulses of short duration it is essential to carefully match the characteristic impedance of the piezoelectric chrystals to backing and loading materia. Also, the examination technique is more difficult and the position of the sampling volume in the vessel is critical. By far, the most commonly used devices in clinical practice are based on CW Doppler.

The Doppler signal can be processed in basically two differenet ways. With the zero-crossing detector, incorporated in most commercial equipments, the average frequency shift is obtained, whereas with spectral analysis the entire Doppler frequency spectrum is displayed. By the latter analyzing technique demonstration of turbulent eddies with low flow velocities in the region of a stenosis is possible.

By positioning the Doppler probe on a position-sensing arm an image, based on physiological data, of the carotid arteries can be constructed (Spencer et al 1974). When the beam from the probe transfixes a blood vessel, and Doppler signals are received, the flow detector delivers a signal which is stored as a spot on a screen. As the probe is moved over the skin overlying the vessel, an image of the projection of the blood vessel is generated on the screen. In one modification the different frequency shifts in various parts of the image are displayed in colour (White & Curry 1978).

Theoretically, Doppler ultrasound may also be used to determine volume flow in a vessel. This calculation is based on two relationships. As evident from the Doppler equation (1), the determination of the true flow velocity within the vessel from the Doppler shift requires the beam-vessel angle (α) to be known. If the mean flow velocity ($\bar{v}$) over the cardiac cycle is known, knowledge about the vessel cross-sectional area (πr^2) permits the volume flow (Q) to be calculated, since

$$Q = \pi r^2 \bar{v} . \quad (2)$$

Although these two relationships may seem simple the exact determination of volume flow is complex because of such factors as axial migration

of red cells and difficulties in precisely assessing the mean velocity, due to amplitude enhancement and nonaxisymmetric flow velocity profile. Nevertheless, some studies have shown that a fairly accurate estimate of volume flow can be obtained by various Doppler techniques (Brodzinski et al 1976, Forsberg 1980). Determination of volume flow is not required for the use of Doppler technique in the detection of stenoses or occlusions in the carotid artery.

Physiological basis of stenosis detection

The signs of carotid disease on which non-invasive diagnosis may be based are due to pathoanatomic and pathophysiologic alterations at the common carotid bifurcation and pathophysiologic changes in distal circulatory beds. Basically, non-invasive tests can be classified as direct if the bifurcation region is examined, and as indirect if the distal circulation is monitored for evidence of more proximal lesions (Ackerman 1979). To evaluate the usefulness of a test its specific attributes and limitations have to be known.

The most common non-invasive methods in current use use indirect tests. These include ophthalmodynamometry, oculoplethysmography, oculosphygmography, thermography and Doppler ultrasound examination of the periorbital vessels. The initial use of Doppler flow-meters in carotid disease aimed at detecting the direction of flow in branches of the ophthalmic artery, as first described by Brockenbrough (1970). In hemodynamically significant stenoses or occlusions flow direction in these periorbital branches may be reversed.

The main limitation of all indirect tests is that they become positive only when a proximal lesion is of hemodynamic significance, i.e. when lumen area is reduced more than about 80 per cent (May et al 1963, Brice et al 1964). Even in the presence of a hemodynamic lesion indirect tests sometimes fail to detect any abnormality because abundant collateral supply to the distal circulatory bed, e.g. via the circle of Willis, has developed. Also, since the lesion itself is not examined a positive finding does not tell whether a severe stenosis or occlusion is present. Despite these obvious limitations, the use of an indirect test as a complement to a direct one may be defended. Most indirect tests are easy to apply and comparatively inexpensive. A positive finding clearly indicates that a lesion is of hemodynamic importance. Also, indirect tests may give evidence of carotid lesions that are located out of reach to be examined by direct techniques.

The detection of bifurcation lesions that are not hemodynamically sig-

nificant requires the use of direct tests. Physiologic information on flow disturbances in the region of a stenosis can be obtained by direct Doppler ultrasound examination whereas anatomic information can be provided by Doppler imaging devices and B-mode scanners.

The application of CW Doppler to the carotid arteries in the neck was at first thought to be impossible, due to difficulties in separating the external and internal carotid arteries. However, Planiol et al (1972) demonstrated that the different characteristics of the flow velocity during the cardiac cycle in the two vessels permitted a reliable separation. Basically, flow in the external carotid artery occurs only during systole whereas flow in the internal carotid artery is antegrade also during diastole, because of the lower resistance of the intracranial vessels than that in the external carotid branches supplying skin and muscle.

With the direct Doppler technique diagnosis of a carotid stenosis is based on the detection of blood flow alterations in the region of the stenosis. Two types of changes may be used for diagnostic purposes. One is an increase in the blood flow velocity across the stenosis and the other is an altered distribution of the different flow velocities within the region of the lesion. With zero-crossing detector analysis of the Doppler signal, only a mean frequency shift is obtained. Thus, with this technique only the increase in mean blood flow velocity can be analyzed. To evaluate the distribution of different flow velocities spectral analysis is required. In normal carotid arteries there is a narrow range of high velocities and only a minimal contribution of the low flow velocities near the vessel wall. In a moderate stenosis there is an admixture of low flow velocities, representing turbulent eddies (Reneman & Spencer 1979). These eddies can be found in the region proximal and (mainly) distal to the stenosis, whereas flow across the stenosis itself probably is laminar. However, because the stenosis usually is short and the Doppler probe is held at some angle to the vessel, mostly not only the stenosis but also the immediately adjacent region is sampled simultaneously.

Doppler examination with continuous-wave technique and zero-crossing detector analysis was the first introduced direct test (Planiol et al 1972) and has been widely applied, mainly in Europe. However, despite almost 10 years of common use precise diagnostic criteria have not been advanced.

Direct Doppler examination is also possible with pulsed Doppler technique (Blackshear et al 1980). Interfaced with a B-scan device the sampling site along the vessel may be closely defined, and a two-dimensional assessment of the inclination angle to the vessel is possible. However, the exact

position of the sampling volume to the middle of the vessel is critical. Also, the size of the sampling volume (width usually 3-4 mm) in relation to the vessel diameter is not negligible. In different patients a variable part of the vessel lumen will be included in the sampling volume.

Apart from the detection of carotid lesions, a Doppler examination may also help to delineate the pattern of collateral circulation in obstructive lesions. This aspect is more fully discussed in relation to Paper IV.

A Doppler imaging device uses evidence of moving blood to construct a profile of the lumen (Spencer et al 1974, Lewis et al 1978). The diagnostic usefulness of this method seems to be limited. The image takes 10 to 20 minutes to construct and is static. Resolution is often poor because of patient movements during the scanning time, errors in the spatial sensing mechanisms of the scanning arm and because time limits that the sweeps of the probe are performed tight enough. In practice, the Doppler imaging device seems to be most useful for providing a track of the lumen along which to position a Doppler probe to obtain selected data on flow velocity.

More precise anatomical information can be obtained by B-scan systems. The B-scanner detects echoes that are related to variations in the acoustical impedance of the tissues. Because of its high resolution (0.5-1 mm) B-scan may identify minimal plaques or ulcerations (Green 1978), but due to physical reasons, a proportion of carotid lesions is not adequately visualized. Some lesions have an acoustical impedance similar to blood (sonolucent lesions), and will not be evident on the B-scan image. Other lesions are not imaged because a calcified plaque in the vessel wall throws an acoustical "shadow" across the lumen, in which other lesions may be hidden. Small plaques or ulcerations may sometimes not be identified because of a partial volume averaging effect. Because the B-scan does not provide any physiological information, a totally occluded carotid artery may not be easily detected. A Doppler probe may be interfaced with the B-scan system, but this combination is not technically easy. B-scan is by far the most expensive direct test. At present, determination of its usefulness must await further data.

Although non-invasive techniques may be an integral part in the clinical evaluation of patients with TIA and stroke, no presently available test can reliably identify small plaques or ulcerations nor provide information on the intracerebral circulation. Angiography remains the definitive diagnostic procedure in patients with stroke symptoms in whom endarterectomy or bypass surgery is considered. However, the information provided by current non-invasive tests may be useful in other settings. Apart from their appli-

cation in some clinical situations in which the indication for angiography is doubtful (cf. above), non-invasive tests may help to identify prognostic features of specific carotid lesions, understand the pathophysiology of carotid lesions and follow the evolution of atherosclerotic lesions with time.

Non-invasive cerebral blood flow (CBF) measurement

Because impairment of the blood flow to the brain tissue is the ultimate cause of the symptoms of carotid arterial disease, both when hemodynamic and embolic factors operate, it might be assumed that measurement of the CBF would contribute to the understanding of the pathophysiology of ischemic stroke.

Kety and Schmidt (1945) introduced the nitrous oxide method to measure CBF, representing a major landmark in the history of cerebrovascular physiology. Much of the basic knowledge about CBF has been gained by its use. The method also permits measurement of the cerebral metabolism. However, the method has its limitations. It is invasive, requiring both arterial and jugular vein puncture, and provides only a mean CBF for both hemispheres.

Because the majority of cerebral diseases, in which information about circulation is important, are focal in nature, it was a significant progress when Ingvar and Lassen (1961) described a method for measuring regional cerebral blood flow (rCBF) in humans. Following intracarotid injection of isotope (initially ^{85}Kr rypton, later ^{133}Xe nenon) the clearance curves are recorded by external detectors. A large body of information on the physiology of the cerebral circulation in health and disease has been accumulated by this method (for a detailed and comprehensive analysis, the reader is referred to reviews such as Olesen 1974 and Fieschi & DesRosiers 1976). The main drawback of the intracarotid injection technique is the necessity for inserting a needle or catheter into the carotid artery, confining its use mainly to patients in whom there is an indication for angiography. In order to overcome this limitation the non-invasive ^{133}Xe nenon-inhalation technique was introduced.

The administration of ^{133}Xe nenon by inhalation was first proposed by Mallet and Veall (1965), and later this technique has been modified, improved and further validated (Obrist et al 1975, Risberg 1980). The non-invasive technique has the considerable advantage of being readily repeatable, enabling changes in rCBF during the course of a brain disorder or of its treatment to be measured.

Two main difficulties are associated with the ^{133}Xe nenon inhalation technique. One is the recirculation of isotope and the second is the contribu-

tion from the airways and from extracerebral tissues to the cerebral clearance curves. However, statistics for dealing with these problems have been successfully developed (Obrist et al 1975, Risberg 1980). The technique allows simultaneous rCBF measurements of both hemispheres. However, this carries with it the risk of cross-over of counts between the hemispheres, tending to underestimate any interhemispheric difference in blood flow (cross-talk) (Risberg et al 1975b). Also, the degree of regional discrimination achieved by the intracarotid technique can not be matched by the inhalation technique.

CBF methods using external scintillation detectors encounters specific problems in patients with cerebrovascular disease, because diffusible indicator methods are not very sensitive to ischemia, whether the isotope is given by inhalation or injection. Scattered radiation (Compton scatter) tends to suppress regional differences, and because the detector system views the tissue as a truncated cone heterogeneous tissue elements are superimposed. In focal ischemia, an adequate amount of isotope may not arrive in the area, in which case counts arriving from adjacent or deeper parts contribute to the clearance curves recorded by the detector (look-through artifact).

In the normal brain, a clearance curve obtained by external detectors can be analyzed for two components, closely representing gray and white matter. However, in pathological states such as cerebral infarction, the difference between CBF of gray and white matter may be small. In the compartmental calculation, CBF of some regions of gray matter may be sufficiently low to be included in the second compartment, so that the relative contribution of the two compartments are not related to the relative anatomic weight of gray and white matter. This phenomenon (slippage) limits the usefulness of compartmental analysis. Also, in order to provide values for flow the partition coefficient for $^{133}\text{Xenon}$ between blood and brain tissue must be known. Because the partition coefficient of abnormal brain tissue is unknown, the analysis of initial slope index (ISI), in the inhalation method calculated from the slope of the head curve from 1 to 2 minutes following the end of the $^{133}\text{Xenon}$ breathing, has been proposed in such instances (Risberg et al 1975a). The ISI has a greater stability to compartmental weight fluctuations than conventional compartmental analysis.

In the interpretation of CBF data in patients with cerebral ischemia, it has to be recognized that a subnormal rCBF does not tell whether the blood flow into the region is restricted due to vascular factors (vessel occlusion, state of collateral pathways and intracerebral vessels) or reflects the reduced demands by functionally depressed or infarcted brain tis-

sue.

The usefulness of non-invasive rCBF measurements in the treatment and care of patients with carotid arterial disease is presently unproven. Clearly, the application of the rCBF method in stroke must take into account the specific problems outlined above, which in part are inherent in the pathophysiological concept of cerebrovascular disease.

OBJECTIVES OF THE PRESENT STUDY

The present study is related to recent developments in therapy and non-invasive diagnosis of carotid arterial disease.

The clinical usefulness of non-invasive tests for carotid lesions depends on the degree of stenosis required to permit detection and the specificity and sensitivity of the test. For the most commonly used direct test, Doppler examination with zero-crossing detector analysis, these data have not been precisely assessed. This information is a prerequisite for the application of the technique in the study of the natural evolution of carotid lesions and their response to surgical treatment, e.g. carotid endarterectomy.

The development of extra-intracranial bypass surgery has generated recent interest in otherwise surgically inaccessible lesions within the carotid and middle cerebral arteries. Of these lesions, carotid artery occlusion is the single most common entity. Because basic knowledge on the natural long term prognosis and the pathophysiological mechanisms involved is incomplete, appropriate selection criteria for bypass surgery have not been established. Also, the possible role of non-invasive rCBF measurement, as part of the diagnostic work-up, has not been assessed.

The present investigations were planned to provide answers to the following questions:

- What is the diagnostic value of non-invasive direct Doppler technique for detecting carotid stenosis and occlusion?
- What is the incidence of recurrent carotid lesions after carotid endarterectomy as compared to the development of carotid stenosis in non-operated vessels?
- What is the natural long term prognosis in carotid occlusion?
- Which pathophysiological mechanisms determine the outcome in carotid occlusion?
- Can non-invasive rCBF studies during rest and induced hypercapnia help to evaluate the capacity of the collateral circulation in carotid occlusion?

A. Direct Doppler examination for detection of carotid lesions (I)

In Paper I the ability of the direct Doppler ultrasound technique to detect extracranial carotid lesions was evaluated in 148 carotid arteries, examined also angiographically. A continuous-wave Doppler device with zero-crossing detector analysis was used in the examinations. With this technique the diagnosis of a stenosis is based on the finding of a local increase in blood flow velocity (cf p 17). The diagnostic value of four quantitative Doppler variables was examined: the maximum systolic ICA (Internal Carotid Artery) frequency, the end-diastolic ICA frequency, the systolic ICA/CCA (Common Carotid Artery) frequency ratio and the end-diastolic ICA/CCA frequency ratio.

In analyzing the results some limitations with the zero-crossing detector became apparent. Due to a non-linear response in higher frequencies and inappropriate mean frequency analysis when spectral broadening is present, the systolic frequency values were found not to be useful in separating normal and stenotic vessels. The use of the end-diastolic frequency values were more appropriate, but the ratio of the end-diastolic frequency values in the internal and common carotid artery was found to be of most discriminating value. Applying this ratio as a diagnostic criterion, all but one of the vessels with a stenosis $\geq 50\%$ (lumen diameter reduction) and in which quantitative Doppler data were obtained had ratios above the normal range (95 per cent confidence interval), all vessels with a stenosis $\leq 50\%$ had ratios within the normal range, and a false positive finding was obtained in only three non-stenotic vessels. The lower limit for the detection of a stenosis was found to be close to 50 % (lumen diameter reduction).

Quantitative Doppler data were obtained for stenoses up to about 75 %. With more pronounced luminal reduction the zero-crossing detector analysis of the increased flow velocities was grossly artifactual, providing a so called "deranged" recording. Nevertheless, the finding of this recording in combination with the auditory finding of very high frequencies, as evident from listening to the Doppler signal, was invariably associated with a severe stenosis.

Although Doppler diagnosis of a carotid occlusion was correct in all vessels but one, it should be noted that the direct Doppler technique (or indeed any other direct or indirect non-invasive test) may not permit a reliable separation of a very severe stenosis and complete occlusion. When a stenosis is severely flow reducing, with only a trickling blood flow left,

the Doppler signal may be of too low amplitude to be detected.

Paper I shows that, with the use of precisely defined diagnostic criteria and a carefully standardized examination procedure, the direct Doppler examination technique with zero-crossing detector analysis is useful. It offers a highly reliable diagnosis of stenoses $\geq 50\%$ and occlusions, whereas it fails to detect stenoses $< 50\%$. The limitations of the zero-crossing detector analysis must be considered in the interpretation of the Doppler data. The method requires some initial practice to be used successfully (equal to other direct tests) but is not unduly difficult to pick up.

What advantages may be gained by application of spectral analysis of the Doppler signal? First, high flow velocities are correctly displayed by spectral analysis, which makes it possible to use systolic frequency data in diagnosis (Spencer & Reid 1979), although it has not been assessed whether this is superior to the use of end-diastolic frequency data. Second, spectral analysis displays the distribution of the different flow velocities within the vessel, analysis of which may serve as a further diagnostic aid, although difficult to assess quantitatively. It seems probable that spectral analysis may be helpful in detecting a proportion of stenoses less than 50 %, but this remains to be documented. Further studies may eventually prove that the finding of retarded blood flow in the stenotic region may have therapeutic consequences in the management of patients with TIA (cf pp 12-13).

The directional Doppler device with zero-crossing detector analysis is fully sufficient in its use as an indirect test, i.e. in the assessment of flow direction in periorbital vessels, preferably the frontal artery (Burjer & Barnes 1977). Although the overall diagnostic yield is inferior to the direct test, the indirect test is easy to apply and the information obtained is supplementary. Therefore, the indirect test should be included in the routine protocol of the carotid Doppler examination.

B. Progression of carotid lesions after unilateral carotid endarterectomy (II)

Little is known about the evolution of new carotid lesions after carotid endarterectomy. There is no report available in which a large number of unselected patients have been examined with repeat angiography after carotid surgery. Because of its invasiveness angiography has mainly been restricted to patients who have developed new ischemic symptoms post-operatively. Based on such selected materials, it is commonly held that the incidence of recurrent stenosis after carotid surgery is low (0.2-4.75 %) (Callow 1980). The Doppler technique described in Paper I provided a method to

determine the incidence of more marked recurrent lesions in an unselected material of patients previously treated with unilateral carotid surgery. The material of patients studied also permitted a comparison of the disease progression in the operated and non-operated carotid arteries, because surgery had mainly been confined to patients, in whom there was a significant lesion only on the operated side.

Doppler examination in the 64 patients available to full follow-up investigation (mean observation period 6 years) revealed a recurrent stenosis ($\geq 50\%$) or occlusion in 36 % of the operated vessels, a figure not significantly different from the proportion of progressive lesions found in the non-operated vessel (27 %). In total, 43.8 % of the patients had developed new lesions in one or both carotid arteries. Average annual stroke rate was 1.6 % on the operated and 0.8 % on the non-operated side. A clear association between the occurrence of new ischemic symptoms and progressive lesions in the appropriate vessels was found: only 5.5 % of the vessels without progressive lesions had associated symptoms, as opposed to about 30 % of the vessels in which new lesions were documented. However, it should be noted that the majority of the carotid arterial disease progression was clinically silent.

The seemingly high incidence of progressive lesions on both sides is not particularly surprising when compared with the natural history of carotid bifurcation atheroma as previously reported. Javid et al (1970) found an increased severity of stenosis in 51 out of 86 patients (59 %) 1-9 years after the first angiography. In 32 patients (38.5 %) the progression in the degree of stenosis exceeded 25 % per year. Bauer et al (1968) examined 49 patients with repeat angiography after a mean interval of 25 months. Progression of lesions was detected in 17 out of 63 carotid arteries (27 %) not operated.

The present data do not allow any firm conclusions to be drawn about the general advisability of carotid endarterectomy in the material of patients studied, because no untreated or medically treated control material was included. However, a comparison with related data in the literature seems to favour carotid surgery to some extent. First, a few studies suggest that a more severe stenosis may have a more grave prognosis than moderate or minimal lesions, and that anti-platelet therapy may be of limited value in these patients (Barnett 1979, Busuttil et al 1980). Second, although there is no precise data available on whether medical treatment with anti-coagulants or anti-platelet drugs may cause carotid lesions to heal, it seems improbable that it will cause a significant regression of severe fibrotic or calcified lesions. Carotid surgery is the only treatment modality

which offers removal of the embolic source. Although a thrombus in the region of a carotid stenosis is less frequently found at arteriotomy when more than one month has passed from the initial symptoms (Harrison & Marshall 1978), the local conditions for the development of new embolic material persists. Furthermore, a severe stenosis harbors the risk of progression toward complete occlusion, which event is associated with the development of a stroke in a proportion of the patients (cf p 27).

A prerequisite for carotid surgery to be considered is that an experienced vascular surgeon is available to ensure an acceptably low complication rate. Calculations by Hass and Jonas (1980), based on data from the Joint Study of Extracranial Arterial Occlusion (Fields et al 1970), suggested a maximal complication rate of 3 per cent for carotid surgery to compete with non-surgical treatment. Surgery is clearly not acceptable when the complication rate exceeds the natural history and precipitate the very stroke outcome that the treatment is intended to prevent.

The high incidence of progressive lesions reported in Paper II emphasizes the important role of careful follow up and control of risk factors after carotid surgery, equal to patients medically treated for cerebral ischemia or with atherosclerosis in other regions. Commonly, carotid occlusive disease, even more than coronary artery disease, is but one aspect of a generalized vascular disorder.

Although data from humans is not available, there are experimental findings to suggest that the administration of platelet-active drugs after vascular injury may prevent the development of arterial lesions. Rats with induced aortic endothelial lesions failed to develop atheromas if they were kept thrombocytopenic (Moore et al 1976). In the cholesterol fed rabbit, Hollander et al (1979) found that aspirin had an inhibitorial effect on the fibrous component of the plaque without preventing the deposition of lipid in the lesions. In a second report from the U S aspirin trial (Fields et al 1978) the clinical effects of aspirin and placebo after carotid surgery were compared. The results favoured aspirin, although significant differences against placebo were not obtained, perhaps partly due to the short observation period (6 months). In fact, the best results concerning prevention of stroke in the entire study was seen in the surgery-aspirin group. However, no data were reported on the surgical complication rate. Although unequivocal support in man is not available, administration of aspirine after carotid surgery at least appears attractive.

C. Acute symptoms in carotid occlusion (III)

The clinical symptoms in carotid occlusion are highly variable, and a certain proportion of the patients develop an occlusion with no clinical abnormality. When symptoms occur, they range from TIA to massive hemispheric infarction. In general, clinical criteria are not useful in indicating the presence of a carotid occlusion.

Of the 59 patients studied in Paper III, the presenting symptoms were: ipsilateral TIA in 12 patients, ipsilateral stroke in 41 patients, and TIA or stroke from other vascular territory than the occluded carotid in 6 patients. 39 per cent of the patients had preceeding TIA referable to the occluded side. Although not specific for carotid occlusion, a characteristic feature of the TIAs were their temporal distribution: they predominantly occurred only shortly (a few weeks) before the occlusion was documented and were usually multiple.

In the present material of patients nine died in the acute phase, in eight of whom the cause of death was related to the stroke. This figure may seem to be a high death rate in the acute phase, but because not every surviving stroke patient with a carotid occlusion is identified and because autopsy is being performed only in selected patients, the true case-fatality rate in carotid occlusion is not possible to determine.

The severity of the presenting ipsilateral stroke in the patients who survived the acute phase was evaluated three weeks after the onset of the symptoms. At that time 14 patients had only slight residual symptoms whereas 18 patients had moderate to severe residua. A substantial recovery later than three weeks was seen in eight patients, in three of whom complete remission of the symptoms occurred.

In interpreting data on carotid occlusion, the selection of the patients included must be borne in mind. Previously, the identification of a carotid occlusion has relied upon angiography or autopsy. In all clinical materials patients presenting with TIA and minor stroke, examined with angiography with the aim of detecting a carotid stenosis accessible to endarterectomy, are probably over-represented. In patients with a moderate to severe stroke the underlying vessel pathology is usually not investigated. In this group of patients angiography is mainly restricted to selected patients, in order to exclude other causes of the symptoms than cerebrovascular (e.g. tumor), or (prior to the CT-era) to rule out the presence of a hematoma in patients with a progressive stroke considered for anticoagulant treatment. No study has been undertaken to determine the prevalence of carotid occlusion in an unselected stroke material or in a population without

stroke symptoms, a task which would be suitable for non-invasive tests.

D. Long term prognosis in carotid occlusion (III)

In Paper III the 50 patients who survived the acute phase were followed for a mean time of 48 months. During this period only two patients had TIA and two patients stroke in the territory of the occluded carotid artery, representing an annual average incidence of about 1 per cent for each. When calculated from life table analysis, similar figures were obtained. One of the patients with a recurrent stroke was later found by Doppler examination to have a recanalization of the occlusion. TIA and stroke referable to other territories than the occluded side was seen in four and three patients respectively.

For comparison, the Table lists all presently available studies on the long term prognosis in carotid occlusion, only the report by Marshall (1966) excluded because the time of follow up is not stated. Both the number of patients included and the time of follow up are variable. The average stroke rate per year was calculated because information to construct a life table is not available in most studies. The total annual stroke rate (irrespective vascular territory) varies between 2.3 and 6.8 %. In half of the studies it is not stated whether new strokes were appropriate to the occluded side or other territories. Four studies includes patients in whom a contralateral carotid stenosis had been treated with endarterectomy, a procedure which may influence the stroke rate also on the occluded side (cf pp 35-36). The study by Fields and Lemak (1976), from the extensive Joint Study of Extracranial Arterial Occlusion, provides the largest number of patients studied. The incidences of stroke on either side are minimum figures: a further 2.7 % each year had new strokes where the side was not known. In the study by Furlan et al (1980) from the Mayo Clinic, a stroke incidence of 2 % on the occluded side was found.

In some studies anticoagulant therapy was given during some time of the follow up period, whereas in other studies precise information on the therapy is not reported. The patients in the study by Fields and Lemak (1976) were given "best available medical therapy", which in an unknown, but probably large number of the patients included anticoagulants. In the study by Furlan et al (1980) 50.7 % and in the present material 40 % of the patients received anticoagulants. Anticoagulant therapy may contribute to a low recurrence rate of stroke, but can conceivably prevent only recurrent symptoms of embolic, as opposed to hemodynamic, origin.

In most studies, including the present, the incidence of death during

Table. Long term prognosis in carotid occlusion

	N	Follow up months	Average stroke incidence, per cent per year		
			Occluded side	Contralateral side	Total
McDowell et al	1961	43	24	?	3.5
Hardy et al	1962	121	44	?	6.3
Dyken et al	1974	43	16.5	?	5.1
Patterson et al	1974	20	30	?	4
Haferkamp	1975	66	59	?	4
Grillo et al	1975	37	36	0	5.4
Fields & Lemak	1976	359	44	2.7 +?	1.4 +?
Andersen et al	1977	28	19	0	0
Heng et al	1978	159	26	?	4.1
Furlan et al	1980	138	60	2	3
Riles et al	1980	50	53	1.8	2.3
Norrvig et al	1981	50	48	1	2.5

* Carotid endarterectomy

follow up exceeds the incidence of new strokes. Most commonly, death is cardiovascular and not cerebrovascular, similar to patients with TIA and stroke in general (Cartlidge et al 1977). Thus, the most critical factor for long term survival after carotid occlusion is the state of the coronary arteries.

E. Pathophysiological mechanisms in carotid occlusion (IV).

Three main mechanisms may theoretically be responsible for the initial clinical symptoms in carotid occlusion. First, ischemic symptoms may be of hemodynamic origin, due to insufficiency of the collateral pathways to maintain an adequate blood flow to the occluded hemisphere. Second, embolism may occur in close proximity to the event of occlusion, either immediately prior to it when the vessel is still open, at the time of occlusion, or closely afterwards before organization of the thrombus has taken place. Third, continuous propagation of the thrombus beyond the circle of Willis may occur.

To determine the relative capacity of the circle of Willis and the ophthalmic artery (the two principal collateral pathways in carotid occlusion), the type of collateral flow, in the initial phase determined by angiography, was correlated with the severity of the clinical symptoms. It was found that all patients with asymptomatic occlusion or only TIA referable to the occluded side had collateral flow via the circle of Willis, and did not utilize retrograde ophthalmic collateral flow. In contrast, half of the patients with stroke on the occluded side had collateral flow via retrograde ophthalmic flow. Five out of six patients, in whom retrograde ophthalmic flow filled the entire territory of the middle cerebral artery, suffered a severe stroke.

Collateral flow to the occluded hemisphere via the two principal pathways is blocked when continuous propagation of the carotid thrombus occurs. The latter case was only documented in four patients, all of whom died in the acute phase because of massive hemispheric infarction with herniation. However, propagation of thrombus in some surviving patients cannot be excluded because of incomplete angiographic studies (cf below).

On initial angiographic examinations, the state of the intracerebral vessels distal to the occlusion was possible to evaluate in 21 out of the 32 patients with stroke on the occluded side. 15 patients had no evidence of intracerebral arterial luminal defect, whereas occlusion of a branch or the main stem of the middle cerebral artery was seen in six patients, five of whom suffered a major stroke. The middle cerebral artery lesions were visualized via contralateral angiography and cross-flow via the circle of

Willis in five of the patients, none of whom had retrograde ophthalmic flow.

On the Doppler examination at the time of follow up, the ophthalmic artery flow pattern was determined. Also, an attempt was made to quantitate flow in the contralateral carotid artery, which would be increased if the contralateral carotid artery served also the occluded hemisphere via the anterior communicating artery. For comparisons with normal flow values, the end-diastolic flow velocity in the contralateral common carotid artery was used, because the deficiencies in the zero-crossing detector analysis of the Doppler signal during other phases of the cardiac cycle precludes the application of any planimetric calculation of mean flow velocity.

In patients with no or only slight retrograde ophthalmic flow an increase in the end-diastolic flow velocity in the contralateral carotid artery of about 60 % and 40 % respectively was found (group means), whereas patients with substantial retrograde ophthalmic flow had no contralateral flow increase. Compared with the initial angiographic examinations, the Doppler examinations revealed a similar collateral flow pattern in the majority of the patients. A change in ophthalmic artery flow was seen in only three patients.

Theoretically, substitution of blood flow velocity data for volume flow requires that the lumen diameter of the vessel is constant between different patients. However, some data suggest that the end-diastolic flow velocity may parallel changes in volume flow rather closely, even if variations in luminal diameter are not taken into account. In a study of femoral artery flow in humans, Mahler et al (1977), utilizing pulsed Doppler technique, found that the diastolic part of the flow recording was the variable which most closely paralleled changes in volume flow. In a study by Risberg and Smith (1980) the correlation coefficient for end-diastolic flow velocity in the internal carotid artery and mean hemispheric CBF measured by inhalation technique was 0.91. In a study on stroke patients a correlation coefficient of end-diastolic flow velocity in the common carotid artery (inclination angle maintained constant) and mean hemispheric CBF was 0.88 (Norrving, Prohovnik & Maximilian, unpublished data 1981).

Paper IV illustrates that, besides the detection of a carotid occlusion, a Doppler examination also permits the type of collateral flow to be delineated by evaluation of the ophthalmic flow pattern and contralateral carotid flow. For natural reasons, preocclusive flow velocity values in the contralateral carotid artery are unavailable, and assessment of an increased flow must rely on comparison with age-comparable normal values. The biological variation inherent in the latter makes any comparison with patients with

carotid occlusion on an individual basis semiquantitative. Doppler examination is less accurate in estimating collateral flow via the vertebral arteries. The latter vessels can only be examined in the region of the atlas slope, where the normal kinking of the vessel makes the inclination angle of the Doppler probe to the vessel unpredictable. In about 50 patients, seen outside this series, the Doppler examination was accurate in predicting the pattern of collateral flow later established by angiography (Norrving, unpublished data, 1981).

It must be pointed out that in most patients in the present material collateral flow via the posterior communicating arteries was not selectively evaluated by angiography. However, from findings in patients outside this series (see also Paper V), extensive collateral supply via this route seems to be rare. This may be so because the diameter of the posterior communicating arteries normally is smaller than the anterior communicating arteries (Sousa Perreira 1974). Also, the posterior communicating arteries is the part of the circle of Willis where developmental abnormalities are most frequently seen (Riggs & Rupp 1963).

The capacity of collateral flow via the circle of Willis depends on its anatomic features but also on the state of the contralateral carotid artery and the vertebro-basilar system. Numerous pathological studies have documented the high prevalence of developmental abnormalities of the circle (e.g. Riggs & Rupp 1963), although some minor alterations should not interfere with the collateral flow capacity. The importance of lesions in extracranial vessels other than the occluded carotid artery will be discussed in relation to Paper V.

Collateral flow to the occluded hemisphere via the circle of Willis is sometimes referred to as "intracerebral steal". However, similar collateral patterns are a feature of arterial occlusive disease in many sites and do not always imply "stealing" of blood. The term "steal" should be reserved for a situation in which an increase in flow to one part of a vascular territory is accompanied by clinical symptoms in another. As confirmed by CBF measurements (V), blood flow to the non-occluded hemisphere is usually adequate even if collateral flow via the circle of Willis fills the entire occluded hemisphere. Another aspect is that continuously increased flow rates in the contralateral carotid artery may unfavourably affect atherogenesis in this vessel with time.

Although hemodynamic factors seem to be the main determinant for the final outcome in the acute phase, some data suggest that a probably large proportion of the initial symptoms may be of embolic origin. In materials

of patients in whom the carotid artery is surgically ligated (e.g. for aneurysm), this procedure is well tolerated in about 75 per cent of the patients (Nishioka 1969). This figure contrasts to the findings in clinical materials with spontaneous atherosclerotic carotid occlusion, in which less than 20 per cent of the occlusions are asymptomatic (Torvik & Jørgensen 1966, III). Although selection bias limits such a comparison, the wide discrepancy suggests additional mechanisms than purely hemodynamic in spontaneous occlusion. Multiple preceeding TIAs, in the present material seen in 40 per cent of the patients, are conceivably caused by microembolism. In patients in whom the state of the intracerebral vessels has been visualized by angiography in the acute phase, luminal defects suggesting emboli were found in 66 per cent and 89 per cent (Pessin et al 1979, Einsiedel-Lechtape 1978). Early angiography is essential to document these emboli, because lysis may occur within a short time. Although precise knowledge about the sequence of events occurring at the time of the occlusion remains elusive, it seems most rational to assume that embolism takes place when the vessel is still open, the origin of the emboli being from a preexisting stenosis. Hypothetically, the flow reduction across a severe stenosis during embolically induced cerebral ischemia may precipitate the development of complete occlusion, in which case the severity of the symptoms will be influenced both by the massiveness of the embolism and by the capacity of the collateral circulation.

Although the pathophysiology in the acute phase is complex and only partly possible to elucidate in retrospect, the study shows that the type of collateral flow is a main determinant for the acute outcome in carotid occlusion, even if the initial symptoms may be caused by embolism. The circle of Willis (mainly the anterior communicating arteries) was found to be the most important collateral pathway, superior in capacity to the ophthalmic artery. The collateral flow via the circle of Willis is mirrored by the ophthalmic flow pattern. In some patients massive initial embolism may cause a severe stroke irrespective of the capacity of the collateral circulation. In a few patients propagation of the thrombus intracranially occurs, which blocks the principal collateral pathways, and seems to be associated with a grave prognosis.

F. rCBF in carotid occlusion (V)

In the preceeding paper conclusions about the adequacy of the collateral circulation were drawn from the relationship between the clinical outcome and the anatomical features of the collaterals, as determined by angiography and Doppler examination. In Paper V the physiological information

supplemented by non-invasive rCBF measurements was analyzed in this respect. rCBF was measured by the ^{133}Xe inhalation technique. Studies were made during the resting condition and, in 20 patients, also during induced hypercapnia.

From the clinical state of the patients, the material was divided into three groups of patients. The distribution of the two principal types of collateral flow (ophthalmic and Willisii type) in the three groups were consistent with the findings in Paper IV, although it should be noted that 13 of the patients were included in both materials.

Both the mean rCBF on the occluded side and the internemispheric asymmetry were found to be related to the clinical state of the patients, and not to the type of collateral flow. Also, there was no apparent correlation between rCBF and the time interval from the initial symptoms within the groups, although in a few of the patients subjected to a second rCBF study 6-12 months after the first, a late increase in rCBF was found.

The finding that the rCBF was mainly related to the clinical state of the patients led to the conclusion that the resting rCBF data were not possible to apply in terms of collateral flow capacity, although insufficiency of the latter may contribute to a subnormal rCBF in some patients. A further support for the conclusion is that several patients with a subnormal rCBF could increase flow substantially during induced hypercapnia.

An ischemic focus was found in less than one third of the patients. A strict definition of an ischemic focus (rCBF less than -2.0 S.D. of the normal intrahemispheric distribution) was adopted in the study; intra- and inter-hemispheric differences of a lesser degree in one or more detectors were more frequently observed, but evaluation of such minor deviations from normality are necessarily more complex and uncertain. However, for reasons more fully discussed in the Paper (cf. also pp 19-20), the regionality of the rCBF method in focal ischemia is limited. Since also the conceptual problem remains, i.e. that primary and secondary flow reductions can not be separated, it is held that clinical decisions about surgical therapy can not possibly rely on the identification of an ischemic focus.

The rCBF response to hypercapnia was found to be more reflective on the hemodynamic features in carotid occlusion than the resting rCBF data. First, some points on the CO_2 response in general and in cerebral ischemia will be considered.

The first factor concerns the shape of the normal $\text{CBF}/p_a\text{CO}_2$ relationship, on which there is no uniformity of opinion in the literature. Both an exponential and linear relationship have been proposed (cf. Olesen 1974,

Purves 1972). However, available reports are based on only two measurements at different $p_a\text{CO}_2$ in each individual, and conclusions about the shape of the relationship have been drawn from pooled data. Although the issue is presently unsettled, this did not seem to affect interpretation of the results in Paper V, because calculation in both ways yielded the same separation into normal and subnormal responses.

The second factor is to what extent the presence of an infarct in itself influences the CO_2 response. Human data in the literature are difficult to evaluate on this respect, because of heterogeneous materials of patients studied, improperly categorized as to the extent of infarction and presence of obstructive lesions (see McHenry 1978). In Paper V the CO_2 response was tested only in patients with no or minor infarction. The presence of a small infarct (at most 3 cm in diameter) did not seem to influence the CO_2 response, and the response also in an ischemic focus paralleled the mean CO_2 response in the middle cerebral artery territory, although this partly may be due to the limited spatial resolution of the rCBF technique.

The third point concerns the speed of the vascular response to CO_2 , which has to be considered because in the present study the CO_2 administration was discontinued for technical reasons during the one minute isotope intake. Reports by Severinghaus & Lassen (1967) and Hauge et al (1980) show that the latent period is barely greater than the lung-to-brain circulation time, and therefore does not significantly influence the present findings.

Thus, it is believed that the various responses obtained during induced hypercapnia are mainly related to the specific hemodynamic features involved in the material of patients studied.

As opposed to the resting rCBF data, the CO_2 response was found to be closely related to the anatomical type of collateral supply, and in concordance with the findings in Paper IV. Thus, all 11 patients with collateral supply to the occluded hemisphere via the circle of Willis and without a stenosis $\geq 50\%$ in the contralateral carotid artery had a normal response. Five out of six patients with the ophthalmic type of collateral flow were found to have an impaired CO_2 reactivity, in addition to the three patients with circle of Willis flow associated with a contralateral carotid stenosis $\geq 50\%$.

The CO_2 response in patients with obstructive cerebrovascular disease has previously been considered mainly to reflect the condition of the intracerebral vessels, i.e. an impaired response would be due to a preexisting "maximal" dilatation on an autoregulatory basis (Fazekas & Alman 1964). However, it is a well established, but often little recognized, physiologic

fact that the hemodynamic effect of an obstructive lesion is dependent on the flow rate (Young et al 1977). When a carotid artery contralateral to an occluded serves both hemispheres flow is increased 40 to 60 per cent (IV), in which case a stenosis of only 40 to 55 per cent lumen diameter reduction will be of hemodynamic importance. These considerations also apply to the collateral flow via the ophthalmic artery.

Thus, an impaired CO_2 response may be due to the state of the intracerebral vessels but also to a limited ability of flow increase in the collateral pathways in themselves. The relative importance of these two factors is not possible to determine from the present findings. However, related data suggest that the perfusion pressure of the intracranial vessels on the occluded side may be significantly reduced already in the resting condition. Comparison between ophthalmic flow direction, assessed by Doppler during carotid compression, and hemispheric collateral perfusion pressure measured intraoperatively during carotid clamping revealed that absence of orthograde ophthalmic flow implied a perfusion pressure < 48 mmHg (Liebman & Barnes 1981), i.e. below the lower range of autoregulation (Fieschi & DesRosiers 1976). Also, during intraoperative measurements in patients with chronic carotid occlusion, low perfusion pressures (down to 9-15 mmHg) in the middle cerebral artery or in a cortical artery have been found (Spetzler & Roski 1980, Collice & Arona 1980).

In conclusion, the resting rCBF data were mainly correlated with the clinical state of the patients and did not allow conclusions about the capacity of the collateral circulation to be drawn. Similarly, the identification of an ischemic focus seems to be of little clinical usefulness, mainly because of methodological factors inherent in the rCBF technique. In contrast, the response to induced hypercapnia seems to constitute the rCBF variable which most closely reflects the hemodynamic features in carotid occlusion. The CO_2 response was closely related to the pattern of collateral flow, in agreement with the results obtained in Paper IV, implying that the adequacy of the collateral supply can to a great extent be deduced from its anatomical features.

G. Possible role of extra-intracranial bypass surgery in carotid occlusion (III, IV, V)

The establishment of precise guidelines for bypass surgery in carotid occlusion is a considerable task and would require also surgically treated patients to be studied. However, from the present findings (III-IV), some limited conclusions about the possible role of bypass surgery seem permitted.

Because of the seemingly favourable natural long term prognosis concerning further stroke on the occluded side (III), it appears that bypass surgery is not indicated as a general prophylactic measure in all patients with a carotid occlusion. Because it is hemodynamically directed, application of the procedure to patients with impaired or only marginally sufficient collateral supply seems more rational.

The capacity of the collateral circulation is in part reflected already in the outcome in the acute phase, for which hemodynamic factors were found to be a main determinant (IV). Thus, a proportion of the patients with impaired collateral supply will suffer a stroke already in the acute phase, at a time when bypass surgery can not be performed. A severe persistent stroke during the subacute-chronic phase has generally been considered to preclude bypass surgery (Spetzler 1979).

However, also after the acute phase a proportion of the patients with a favourable acute outcome could be identified to have impaired collateral flow capacity, as deduced from the finding of an impaired CO_2 response on rCBF measurements (V). The collateral flow capacity was found to be closely related to the prevailing anatomical type of collateral flow, being impaired in patients with retrograde ophthalmic flow and in patients with circle of Willis flow associated with contralateral carotid stenosis $\geq 50\%$ (lumen diameter reduction).

Thus, a possible role of bypass surgery in carotid occlusion may be to improve the vascular reserve capacity in patients with the two types of collateral pattern associated with an impaired CO_2 response. However, further studies, including surgically treated patients, will be required to determine the actual benefit of the procedure in these patients. It can not be directly assumed that a bypass would be a more efficient collateral than the ophthalmic artery; it might merely redistribute blood flow from the latter vessel. In patients with anatomically patent circle of Willis but impaired collateral supply via this route because of a contralateral carotid stenosis of hemodynamical importance, an endarterectomy of the stenosis is an alternative procedure which may well be more effective than a bypass from a hemodynamic point of view.

Bypass surgery as a prophylactic procedure is mainly applied with the presumption that a significant number of post-occlusion ischemic events are hemodynamically related. Presently available data are incomplete, but some observations argue against an uncritical acceptance of the hemodynamic concept. Embolism from arterial lesions in extracranial arteries other than the occluded carotid and supplying the occluded hemisphere, or from the distal

"tail" of the occlusion may occur. The proximal "stump" of the occluded carotid artery has been suggested as an important source of emboli responsible for post-occlusion ischemic events (Barnett et al 1978). However, this presupposes a collateral supply via the ophthalmic artery, a collateral source in the present study found to be of limited capacity in itself. When post-occlusion ischemic events are believed to be of embolic origin, a direct surgical approach (common and external carotid endarterectomy on the occluded side, obliteration or resection of a "stump") to an identified lesion or medical treatment with anticoagulants/anti-platelet drugs may be considered, if there is angiographic demonstration of blood supply from the area of the lesion to the occluded hemisphere (Heros & Sekhar 1981).

Occasionally, recanalization of a carotid artery occlusion occurs (III, Sinderman et al 1974, Markvalder et al 1980). Perhaps the most important aetiology in these patients is spontaneous carotid dissection, which most commonly affects the extracranial part, may result in total occlusion (Gee et al 1980, Cusick & Daniels 1981) and has a strong tendency of spontaneous resolution (Ehrenfeldt & Wylie 1976, Gee et al, 1980). This entity should be considered in younger patients with carotid occlusion and no obvious predisposing condition. It might be advisable to repeat the angiography after an interval before the final decision on surgical therapy is made.

It should be noted that the principles enunciated on the possible application of bypass surgery pertain only to carotid artery occlusion. They should not be extended to include other arterial lesions that may be considered for the bypass procedure. In the latter lesions both the natural long term prognosis and the pathophysiology are likely to be considerably different from the features of internal carotid occlusion.

GENERAL CONCLUSIONS

1. Non-invasive direct Doppler examination of the carotid bifurcation is useful for detection of carotid arterial disease. The lower limit for the detection of a stenosis is close to 50 per cent (lumen diameter reduction). Sensitivity for stenoses ≥ 50 per cent or occlusions was 98.3 %, and specificity for stenoses ≤ 50 per cent or normal vessels was 96.6 %.

2. After unilateral carotid endarterectomy a considerable, but mostly clinically silent, progression of carotid lesions occurs both in the operated and non-operated carotid arteries. In 64 patients previously treated with unilateral carotid endarterectomy, direct Doppler examination at the time of follow up (mean 6 years after surgery) revealed a recurrent stenosis ($\geq 50\%$) or occlusion in 37 % of the operated vessels, a progression rate not significantly different from that found in the non-operated carotid artery (27 %). Almost one third of the progressive lesions were associated with symptoms of TIA or stroke, as opposed to only 5.5 % of vessels without progression of lesions ($p < 0.001$).

3. In 50 surviving patients with carotid occlusion followed for a mean of four years, a low annual incidence of further stroke (~ 1 %) and TIA (~ 1 %) on the occluded side was found. Anticoagulant treatment in 40 per cent of the patients may have contributed to the low recurrence rate.

4. The acute outcome in carotid occlusion is closely related to the type of collateral flow. The anterior circle of Willis was found to be the most important collateral pathway, superior in capacity to the ophthalmic artery. The collateral flow capacity via the circle of Willis is mirrored by the ophthalmic flow pattern. Irrespective of the collateral flow capacity a severe stroke may occur in some patients as a result of a massive embolism, and in a few patients propagation of the thrombus beyond the circle of Willis occurs.

5. rCBF measurements by the non-invasive $^{133}\text{Xenon}$ inhalation technique in 39 patients with subacute-chronic unilateral carotid occlusion revealed as an almost constant finding an interhemispheric asymmetry, which was related to the severity of the cerebral lesion and not to the type of collateral flow. An ischemic focus was rarely identified with the technique used. The CBF response to induced hypercapnia seems to be the variable most closely reflecting the collateral hemodynamic features in carotid occlusion. An impaired CO_2 response was found in patients with retrograde ophthalmic flow and in patients with circle of Willis flow associated with a contralateral carotid stenosis ≥ 50 per cent.

ACKNOWLEDGEMENTS

The study was carried out at the Department of Neurology, University Hospital, Lund, Sweden.

The accomplishment of this work was made possible by the kind help of many persons, all contributors to positive experience. In particular, I am indebted to my two supervisors;

Professor Ragnar Müller, who introduced me to cerebrovascular research, and throughout the study provided support and penetrating criticism; and

Docent Bengt Nilsson, inspirator and close collaborator, whose rare scientific abilities lent coherence to my thoughts and writings.

I also owe a specific debt of gratitude to Dr Patrick Smith, Pau, France, for expert tuition in Doppler technique and warm generosity during my stay in France.

I am happy to thank the co-authors Drs Sten Cronqvist, Jan-Edvin Olsson and Jarl Risberg for generous collaboration and stimulating discussions.

Mrs Asta Tykesson provided admirable assistance in typing the manuscript. Mrs Karin Andersson helped me in the tedious search for patient files.

The appreciation for my family, in supporting me in this work, is greater than cold offset print can convey.

Part of the study was supported by a grant from the Elsa Schmitz' Foundation.

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DOPPLER EXAMINATION OF THE CAROTID ARTERIES

A comparative study with angiography

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ABSTRACT

The ability of Doppler ultrasound to detect extracranial carotid arterial disease was evaluated in 148 carotid arteries, examined also angiographically. A continuous wave, directional Doppler with zerocrossing meter was used. Doppler diagnosis was based on direct examination of the carotid bifurcation. Of four quantitative variables evaluated, only the end-diastolic ICA/CCA frequency ratio was found to be useful. In stenoses exceeding 75 % a deranged Doppler recording was obtained. For stenoses ≥ 50 % or occlusion sensitivity was 98.3 %, specificity 96.6 % and over-all accuracy 97.3 % with the direct examination technique. Corresponding figures for an indirect Doppler test (frontal artery flow) was 45.8 %, 100 % and 78.4 %. Stenoses < 50 % could not be separated from normal vessels. Direct Doppler examination with a zerocrossing detector is reliable, provided that the limitations of the frequency analysis are considered.

INTRODUCTION

The importance of atheromatous carotid lesions in the pathogenesis of supratentorial TIA and stroke is well recognized. The majority of the lesions occurs within the extracranial part of the internal carotid artery, mainly within the proximal 2 cm (Hass et al. 1968). Although angiography still remains the definitive diagnostic method, the expense and the small but definitive, risk of this procedure have prompted the development of non-invasive techniques for the diagnosis of carotid artery disease.

The non-invasive methods most commonly used today are indirect tests which monitor the orbital circulation for evidence of proximal carotid disease. These tests include peri-orbital Doppler sonography, ophthalmodynamometry, oculo-sphygmography and thermography (cf. Ackerman 1979). The limitations of the indirect tests are that they can detect only hemodynamically significant lesions. A carotid lesion is of hemodynamic importance only when the lumen area is reduced about 80 % or more, corresponding to a residual lumen diameter of less than 1.5-2 mm (Brice et al. 1964, May et al. 1963, deWeese et al. 1970). Also, indirect tests cannot differentiate between a high-grade stenosis and complete occlusion.

The use of a direct test, in which the site of the lesion is examined, is desirable because it can identify a lesion to the extracranial part of the carotid artery and may also detect moderately severe stenoses that do not reduce volume flow.

The continuous wave Doppler method utilizing a zero-crossing detector for frequency analysis is most commonly used because the device is readily commercially available at low cost. After the introduction of this method on the carotid arteries by Planiol and Pourcelot (Planiol et al. 1972) its diagnostic value has been documented (von Reutern et al. 1976, Orgogozo et al. 1978, Bes et al. 1979). However, the assessment of the Doppler findings has partly been qualitative and precise diagnostic criteria delineating normal or moderately stenosed vessels have not been stated.

In this study various objectively defined Doppler variables have been analyzed for the diagnostic value in predicting extracranial carotid arterial

disease as established by angiography in 148 carotid arteries.

MATERIAL AND METHODS

The study was performed on data from 148 carotid arteries in 86 patients who had been examined with both angiography and Doppler for the detection of extracranial carotid artery disease. The time of the two examinations was not separated by more than one week. In 78 patients the Doppler examination was performed before and in eight patients after the angiography. The patients were seen during a two-year period (February 1979 - February 1981). All patients had clinical symptoms of TIA or stroke within the carotid territory. Angiographies were performed mainly to identify possible surgical lesions and, in a few patients, to exclude other etiology of the symptoms than cerebrovascular. Mean age of the patients was 56 years (range 27-74 years). The material includes all patients in whom both examinations were performed during the time period studied. The Doppler and angiographic findings were independently assessed in retrospect.

Doppler examination

The Doppler examinations were performed with a Parks continuous-wave directional Doppler Model 906 (Parks Electronics Lab., Beaverton, Oregon) in which the average frequency of the Doppler frequency spectrum is determined by a zero-crossing detector. An emitting frequency of 9.7 MHz was used. The frequency analyzed Doppler signal was recorded on a Mingograph (Elema-Schönander, Solna, Sweden) at 25 mm s^{-1} . Calibration tests at known frequency shifts and known velocities had been performed previously (Forsberg and Olin 1980).

The patients were examined in a standardized procedure in the supine position after 10 min rest. The Doppler probe, placed against the neck with intervening coupling jelly (Aquasonic^R), was held gently to the skin to avoid external compression of the examined arteries. The common, internal and external carotid arteries were examined along their extracranial course during continuous auditory control via headphones. The features of the velocity recording (and also the audio-signal) permit a reliable differentiation between the external and the internal carotid arteries without the use of an imaging technique (Planio et al. 1972). In brief, flow in the external carotid artery occurs only during the systolic phase whereas flow in the internal carotid artery is antegrade also during diastole.

The Doppler probe was directed head-wards and was positioned at 45°

angle to the skin. In the earlier part of the series this was controlled by manual measurement whereas in the later part a specially developed probe holder was used to maintain a constant angle (Forsberg and Olin 1980). Because no method for the precise determination of the inclination-angle to the vessel was available in this study, only the values of the Doppler frequency shifts (in KHz) were used, both for the common and internal carotid artery.

Recordings were made from the common and internal carotid arteries at defined points. In the common carotid artery Doppler frequencies were recorded about 1.5 cm proximal to the carotid bifurcation. In internal carotid arteries without local frequency increase, recordings were made about 2 cm distal to the bifurcation. In vessels with a local increase in the frequency the probe was positioned at the point where the highest frequencies were found. Care was taken not to include any venous signal in the arterial recordings. In the occasion of a vein overlying the artery, the vein was gently compressed 2-3 cm in cephalic direction to the examination site. From the recordings the systolic and the end-diastolic frequencies were obtained (Fig. 1 a) and the quotients between the corresponding frequencies in the internal and the common carotid arteries were calculated (systolic and end-diastolic ICA/CCA frequency ratio).

In some vessels with very high local frequencies, as evident from the audio-signal, the frequency recording was irregular without the normal phasic wave-form (Fig. 1 b). This was designated as a deranged recording, which could not be assessed quantitatively.

A diagnosis of internal carotid artery occlusion was made when this artery could not be detected in its normal location. In patients with carotid occlusion collateral flow from the external carotid artery can be established via retrograde flow in the ophthalmic artery. When this collateral flow is abundant, proximal external carotid artery branches may show antegrade diastolic flow, which normally is a feature of only the internal carotid artery. However, separation from the internal carotid artery can be obtained by compression of the different external carotid branches distal to the examination site (Büdingen et al. 1976).

The Doppler examination also included an indirect test, the diagnostic value of which was compared to the direct carotid measurement. As indirect test flow direction in the frontal artery above the inner canthus of the eye was determined (Müller 1972, Burger and Barnes 1977). The flow direction could be clearly identified as ortograde (out of the orbit) or retrograde (into the orbit) in each patient. No patient with zero flow over the frontal

Table 1. Results of the direct and indirect (frontal artery flow) Doppler examinations compared with angiographic findings in 148 carotid arteries

	Direct Doppler examination			Frontal artery flow	
	normal	stenosis ≥ 50 %*	occlusion	ortograde	retrograde
Angiographic findings:					
normal	77	3	-	80	-
stenosis < 50 %	9	-	-	9	-
stenosis ≥ 50 %	1	33	1	26	9
occlusion	-	-	24	6	18

*Criteria: end-diastolic ICA/CCA frequency ratio > 2.0 or deranged recording.

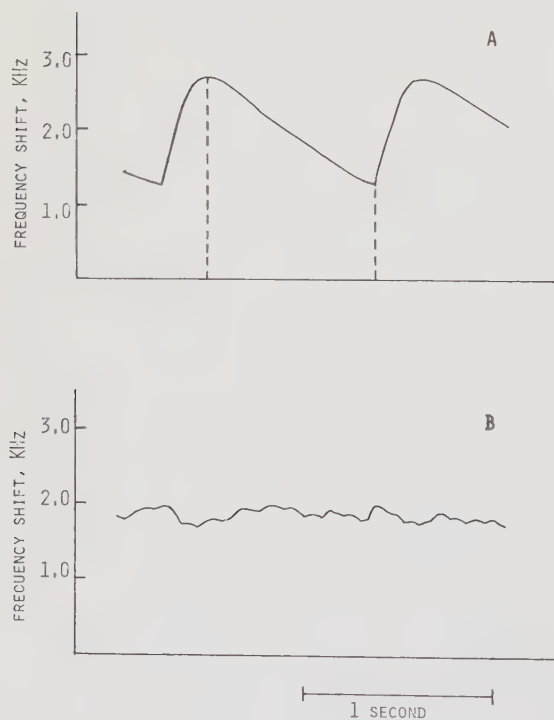


Fig. 1 a. Flow velocity recording in a normal carotid artery. Maximum systolic frequency and end-diastolic frequency are indicated.

b. Deranged recording.

artery was seen in this series.

Angiography

Angiographies performed were aortic arch angiography in 26 patients or selective common carotid angiography, unilateral in 24 patients and bilateral in 36 patients. In normal internal carotid arteries the lumen was measured at a point about 2-3 cm distal to the bifurcation. Three internal carotid arteries with wall irregularities not measurably diminishing lumen diameter were included in the angiographically normal group. In carotid arteries with stenotic lesions the minimum diameter at the stenosis was measured utilizing all available projections. For the calculation of the percentage lumen reduction, the diameter in the involved area and the diameter in the angiographically normal area, generally 2-3 cm more distal, were used. Occlusion refers to complete obstruction of the internal carotid artery.

RESULTS

Angiographic and Doppler findings were compared in 148 carotid arteries. Angiography was normal in 80 vessels, showed a stenosis $< 50\%$ in 9 vessels, a stenosis $\geq 50\%$ in 35 vessels and a carotid occlusion in 24 vessels. Mean lumen diameter in normal carotid arteries was $6.1 \text{ mm} \pm 0.72 \text{ (S.D.)}$.

The diagnostic value of four quantitative Doppler variables was examined: the systolic ICA frequency, end-diastolic ICA frequency, the systolic ICA/CCA frequency ratio and the end-diastolic ICA/CCA frequency ratio. The Doppler findings of a deranged recording, not possible to analyze quantitatively, and internal carotid artery occlusion were evaluated separately.

Figure 2 a-d gives the relationships between the residual lumen diameter, determined angiographically, and the four quantitative Doppler variables. The normal range, defined as the 95 % confidence interval ($\text{mean} \pm 2 \text{ S.D.}$) for each variable in normal vessels, is indicated in the Figure. Because it has been suggested that a stenosis of approximately 50 % is required before a change in mean velocity may be detected (Ackerman 1980), vessels with a stenosis $< 50\%$ and $\geq 50\%$ were indicated separately.

For systolic ICA frequencies a large overlap in the values of normal and stenotic vessels exists: 13 out of 18 vessels with a stenosis exceeding 50 % fell within the normal range (Fig. 2 a). With the formation of the systolic ICA/CCA frequency ratio (Fig. 2 b) separation was not improved.

Figure 2 c relates the end-diastolic ICA frequency to the residual lumen

△ = STENOSIS < 50 %

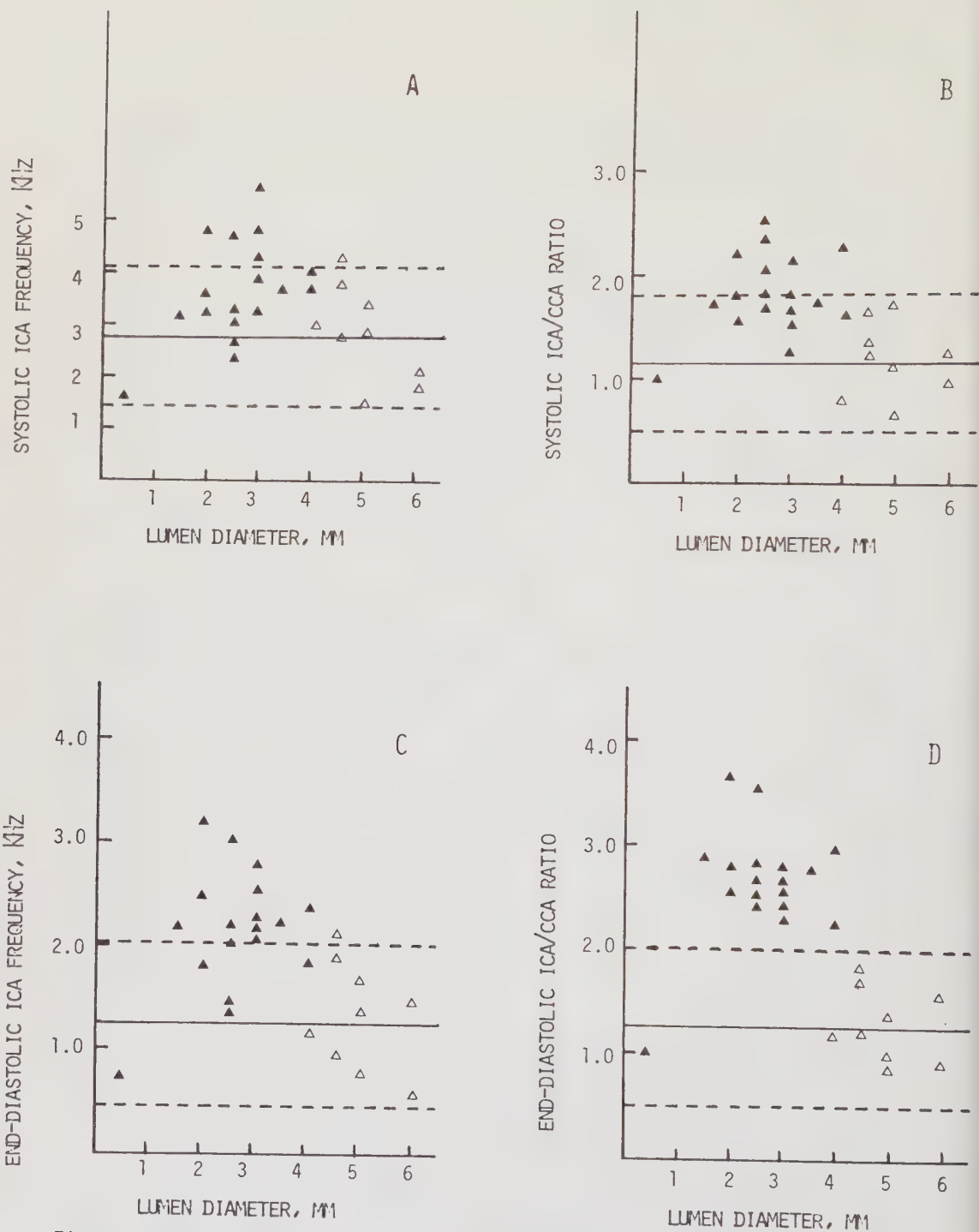


Fig. 2. Lumen diameter (determined angiographically) related to four quantitative Doppler variables: a) systolic ICA frequency, b) systolic ICA/CCA frequency ratio, c) end-diastolic ICA frequency, d) end-diastolic ICA/CCA frequency ratio. Mean values (solid lines) and 95 % confidence interval (broken lines) in normal vessels are indicated for each variable.

diameter. Although discrimination is better than for maximum systolic frequency, 5 out of 18 vessels with a stenosis $\geq 50\%$ had values within the normal range.

The end-diastolic ICA/CCA frequency ratio was found to be of most discriminating value (Figure 2 d). All but one of the vessels with a stenosis $\geq 50\%$ had a ratio above the normal range (1.24 ± 0.76). A false positive Doppler finding, i.e. a ratio above the upper 95 % confidence limit, was found in only three non-stenotic vessels, two of which in one patient. Angiography in this patient showed an anomalous course with marked tortuosity of the internal carotid artery on both sides. In vessels with a stenosis less than 50 % ratios within the normal range were found. In one vessel with a very tight stenosis (residual lumen less than 0.5 mm) a normal ratio was obtained. The bifurcation in this case was located low in the neck, partly hidden by the sternocleidomastoid muscle. On the first Doppler examination the proximal part of the internal carotid artery was incorrectly taken for the common carotid artery. On re-examination after angiography a deranged recording was obtained at the site of the stenosis.

Figure 3, which relates the end-diastolic ICA/CCA frequency ratio to percentage lumen reduction determined angiographically, further confirms that the lower limit for the detection of a stenosis is close to 50 %. Quantitative Doppler data were obtained for stenoses up to about 75 %.

A deranged recording in the internal carotid artery was obtained in 16 vessels. This finding was invariably associated with a severe stenosis (mean residual lumen diameter 1.5 mm, mean percentage lumen reduction 78 %).

The Doppler diagnosis of an internal carotid artery occlusion was correct in 23 out of 24 vessels. In one vessel angiography, performed one week before the Doppler examination, showed a very severe stenosis with residual lumen less than 0.5 mm. Whether complete occlusion may have occurred during the time interval between the two examinations is unproven.

The results of the various Doppler criteria (end-diastolic ICA/CCA frequency ratio > 2.0 , deranged recording and internal carotid artery occlusion) compared with angiography are summarized in Table 1, which also gives the results of the indirect test (flow direction in the frontal artery). The direct examination technique correctly identified 58 out of 59 vessels with a stenosis $\geq 50\%$ or occlusion, a sensitivity of 98.3 %. Eighty-six of 89 vessels with stenosis $< 50\%$ or without stenosis were correctly identified, a specificity of 96.6 %. The over-all accuracy was 97.3 %. For the indirect test sensitivity was 45.8 %, specificity 100 % and over-all accuracy 78.4 % for stenoses $\geq 50\%$ or occlusion.

END-DIASTOLIC ICA/CCA RATIO

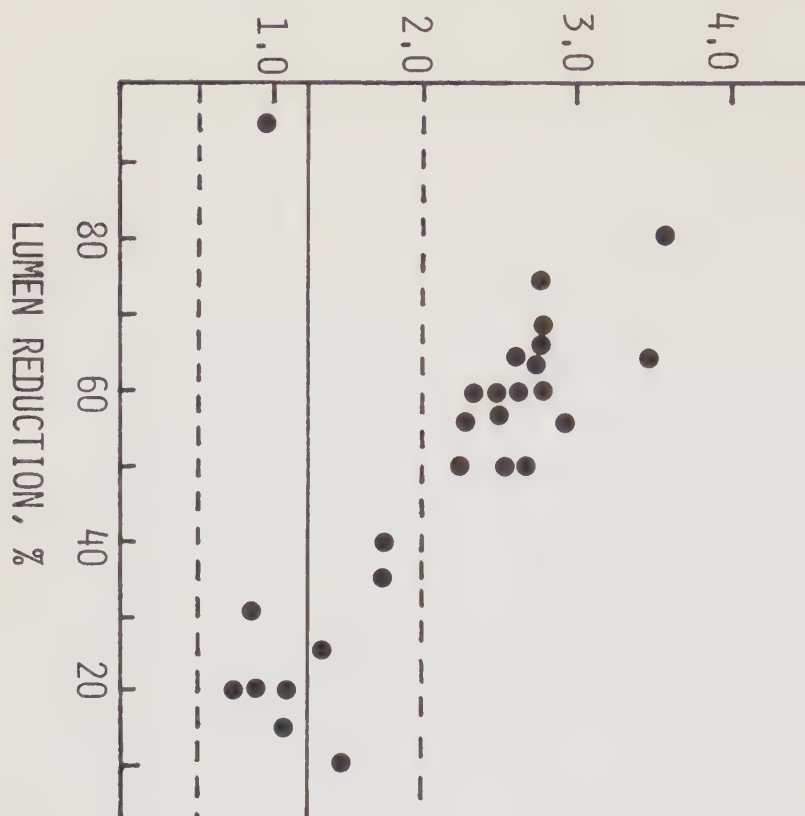


Figure 3. Percentage lumen reduction (determined angiographically) related to end-diastolic ICA/CCA frequency ratio. Normal range and mean value indicated as in Fig. 2.

DISCUSSION

The diagnosis of stenotic lesions by direct examination of the carotid arteries is based on the detection of flow disturbances at the site of the narrowing. The theoretical relationship between residual lumen and the blood flow velocity has been outlined by Spencer and Reid (1979). At the point of stenosis flow velocities and the corresponding maximum Doppler frequencies increase with progressive narrowing. Furthermore, due to turbulent eddies near the stenosis, a broadening of the frequency spectrum can be found (Reneman and Spencer 1979). Although this may be evident when listening to the audio-signal, objective evaluation requires spectrum analysis which was not utilized in this study.

Of the four quantitative variables that were examined for their diagnostic value to detect carotid artery disease, only the end-diastolic

ICA/CCA frequency ratio was found to be useful.

The lesser discriminating value of the systolic frequency can be explained by the limited accuracy of the zero-crossing detector in the flow situation in or near a stenosis. First, the true maximum systolic frequencies found even in a moderately severe stenosis are above the range in which the output of the zero-crossing detector is linear (Woodcock 1975, Spencer and Reid 1979, Forsberg and Olin 1980). Second, the wide range of frequencies seen in the region of a stenosis makes the determination of the mean frequency inaccurate (Flax et al. 1974). The low frequencies, due to turbulence and vessel wall movements, are of high amplitude which outweighs the low amplitude of the high frequencies (Reneman and Spencer 1979). With marked narrowing of the vessel the high frequencies may be entirely lost, which relates to the finding of a deranged recording without pulsatile characteristics (Strandness 1978). Third, differences in flow velocity profile will affect the mean frequency analysis by the zero-crossing detector (Lunt 1975).

For each of these factors the use of the end-diastolic frequency, instead of the systolic, offers advantages. The end-diastolic frequencies are within the linear range of the zero-crossing detector (Woodcock 1975, Forsberg and Olin 1980). Flow disturbances due to turbulence are less pronounced during the diastolic than the systolic phase (Reneman and Spencer 1979). Also, during the diastolic phase a more flat velocity profile is seen (McDonald 1974, Peronneau et al. 1974).

The end-diastolic ICA/CCA frequency ratio was more discriminating than the absolute end-diastolic frequencies in the internal carotid artery. The overlap in absolute frequencies in normal and stenotic vessels can be attributed to individual variations in vessel size, elasticity and volume flow (related to the cerebral blood flow). Because these factors should affect both the common and internal carotid artery the formation of a ratio would diminish their influence.

In this study the inclination angle to the skin was maintained constant at 45° . Whereas the common carotid artery normally runs parallel to the skin, the internal carotid artery usually courses at a different angle. Usually, the internal carotid artery is examined at a smaller inclination angle than the common carotid artery (Blackshear et al. 1980). However, the frequency* induced by a moderate to severe stenosis usually exceed the influence of the variations in inclination angles to the internal carotid artery. A ratio above the normal range was obtained in three of 80 normal vessels only.

The appropriate determination of the maximum systolic frequencies re-

quires the use of spectrum analysis, which has been utilized by Spencer and Reid (continuous-wave technique) (Spencer and Reid 1979) and Blackshear and co-workers (pulsed Doppler technique) (Blackshear et al. 1980). The latter applied the ratio of the mean peak ICA velocity to mean peak CCA velocity as a diagnostic criterium. They found a ratio below 0.8 in normal vessels and above 1.5 in all high-grade stenoses (exceeding 60 %). The corresponding values for the end-diastolic frequency ratio in this study were both higher: 1.24 and 2.00 respectively. However, corrections for the ICA inclination angle (determined by B-scan imaging) were performed by Blackshear et al. (1980). An additional explanation may be that the increase in the end-diastolic and maximum systolic frequencies in a stenosis is not directly proportional.

A carotid occlusion could be correctly identified by Doppler except in one vessel in which angiography showed a very severe stenosis. Because angiography was performed one week before the Doppler examination, the possibility remains that complete occlusion may have occurred in the time interval between the two examinations. However, theoretically it may indeed be impossible to separate a very tight stenosis from a complete occlusion by Doppler examination. In a stenosis flow velocities increase with progressive narrowing. However, above a certain degree of stenosis (residual lumen less than about 0.5 mm) the increased resistance over the stenosis will make the flow velocities fall (Spencer and Reid 1979). When this degree of narrowing is reached the flow signal may be of too low amplitude to be detected. The rare occurrence of such a very tight and severely flow reducing stenosis is probably due to its transient state with rapid development into complete occlusion.

The advantages of the direct measurement at the site of a lesion to indirect measurement of the orbital circulation are clearly indicated in this study. The direct technique usually permits discrimination between an extracranial stenosis and occlusion, and also moderately severe stenoses can be detected. However, the information obtained by the indirect examination should not be disregarded, because a pathological finding indicated that a proximal lesion is of hemodynamic significance. A pathological finding may also be obtained in intracranial carotid lesions proximal to the ophthalmic artery, a region not possible to examine by direct technique. In patients with carotid artery occlusion, determination of the ophthalmic artery flow is important for the evaluation of the collateral flow pattern (Norrving et al. 1981).

With the use of the diagnostic criteria outlined above (end-diastolic

ICA/CCA frequency ratio > 2.0 , deranged recording and ICA occlusion) an overall diagnostic accuracy of 97.3 % for stenoses ≥ 50 % and occlusions was obtained. Although the full characterization of the flow disturbances in the region of a stenosis requires spectral analysis, the present study shows that the far more simple direct Doppler technique with a zero-crossing detector is reliable, provided that the limitations of the frequency analysis are considered.

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CAROTID DISEASE PROGRESSION AFTER ENDARTERECTOMY:
A Doppler ultrasound study

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In part presented at the Satellite Symposium on Pathophysiology and Pharmacotherapy of Cerebrovascular Disorders, July 22-25, 1980 in Tübingen, West Germany

ABSTRACT

The clinical prognosis and evolution of new carotid lesions after unilateral endarterectomy were determined in 64 patients, with a mean observation period of 6 years. Surgery was mainly confined to patients with a significant stenosis only on the appropriate side. Average annual stroke rate was 1.6 % on the operated and 0.8 % on the non-operated side. Direct Doppler examination of the carotid bifurcation at follow up revealed a recurrent stenosis (≥ 50 %) or occlusion in 36 % of the operated carotid arteries, not significantly different from the proportion of progressive carotid lesions on the non-operated side (27 %). In total, 43.8 % of the patients had developed new lesions in one or both carotid arteries. About 30 % of the progressive lesions were associated with symptoms of TIA or stroke, as opposed to 5.5 % of vessels without progression of lesions. Although mostly clinically silent, the considerable progression of carotid lesions emphasizes the importance of careful follow up and control of risk factors after carotid surgery.

INTRODUCTION

The relationship between extracranial carotid disease and cerebral and/or retinal ischemia is well established and, in selected patients, carotid thrombendarterectomy is widely applied. The assessment of its therapeutic value is mainly based on the incidence of new ischemic events during the next few years after surgery as compared to the course in untreated or medically treated patients. The evolution of carotid lesions per se, whether operated upon or not, have been less well documented, mainly because angiographic examinations during follow up have been restricted to patients with new ischemic symptoms.

In the present study we have evaluated the incidence of recurrent carotid stenosis following operation as well as the evolution of carotid lesions in untreated arteries, and the relationship between these changes and the occurrence of new cerebral ischemic episodes. We thus report the long-term clinical and vascular prognosis in patients operated with unilateral carotid endarterectomy. Both carotid arteries were angiographically examined pre-operatively and the majority of the patients had post-operative angiography. The long-term disease progression on both sides were determined by Doppler ultrasound examination.

MATERIAL AND METHODS

The basis of the study is a material of 104 patients operated with unilateral carotid endarterectomy during the period 1966-1978. 64 patients were available to full follow-up investigations during 1979-1980.

The patients were initially examined and selected for operation at the Department of Neurology, University Hospital, Lund. Mean age of the patients were 60 years (range 40-77 years). The ratio male/female was 71/33. Treated hypertension was present in 52 %, diabetes in 13 % and hyperlipemia in 5 %. A history of previous myocardial infarction was obtained in five patients. Three patients had angina pectoris and six patients had claudicatio inter-

mittens.

All patients had ischemic symptoms from the carotid territory: hemispherical TIA and/or transient monocular blindness were at hand in 38 and minor stroke in 66 patients.

Angiographic examinations included selective common carotid arteriography on the appropriate side and aortic-arch angiography. To be considered for surgery, the patients should have significant lesions in the appropriate internal carotid artery and, with few exceptions, insignificant changes in other extracranial vessels or intracranially. Table 1 details the angiographic findings on the appropriate (op) and the contralateral (ctr) side.

Table 1. Pre-operative angiographic findings in 104 patients

	op side	ctr side
Angiography:		
normal	-	46
plaque/stenosis < 50 %	30	53
stenosis $\geq$ 50 %	74	1
occlusion	-	4

Carotid endarterectomies were performed at the Department of Thoracic Surgery. General anesthesia and continuous EEG monitoring were used. The operative complications were: death 3 patients (stroke 2, myocardial infarction 1), non-lethal stroke 7 patients and TIA 8 patients.

Anticoagulant therapy was given from the time of the initial symptoms and continued 2-3 months postoperatively. Within 2-3 weeks after surgery, 81 patients had a post-operative common carotid angiography demonstrating a "normal" post-operative appearance in 70, stenosis $\geq$ 50 % in 4 and occlusion in 7 patients.

Among the 101 surviving patients, further records from seven patients were incomplete. During the follow-up period 30 patients had died: 1 from stroke on the contralateral side, 17 from myocardial infarction (in this group 1 stroke was registered on the op side, 1 at the ctr side and 1 within the vertebro-basilar territory), 4 from other cardiovascular disease, and 8 from other causes. Thus, 64 patients remained for full follow-up examination.

The follow-up examinations during 1979-1980 included clinical neurological examination and Doppler ultrasound examination with a Parks continuous wave directional Doppler Model 906 (Parks Electronics Lab., Beaverton, Oregon) at an emitting frequency of 9.7 MHz. The common, internal and external carotid

arteries were examined along their extracranial course (4). Velocity curves, recorded on a Minograph (Elema Schönander, Solna, Sweden), were obtained from each patent vessel. The diagnosis of stenosis or occlusion was based on the findings of direct Doppler examination in the bifurcation region. Criteria for a stenosis finding were either an end-diastolic ICA/CCA ratio > 2.0 (moderate stenosis) or deranged recording in patients with very high local flow velocities and turbulence (severe stenosis). In a previous methodological study (12), the lower limit for the detection of a stenosis with this technique was found to be approximately 50 % (lumen diameter reduction). Sensitivity for stenoses ≥ 50 % or occlusion was 98.3 %, and specificity for stenoses < 50 % or vessels with no stenosis was 96.6 %. The direct Doppler examination usually permits separation of severe stenosis and complete occlusion.

RESULTS

The mean observation period of the 64 patients at disposal to follow-up examination was 6 years (range 1-13 years).

During the follow-up period 5 patients had TIA and 6 patients stroke on the operated side, whereas 2 had TIA and 3 stroke on the contralateral side (5 had vertebro-basilar symptoms). The ischemic symptoms appeared approximately at random during the observation period, i.e., without any evident relation to the time of the operation. The average annual incidence of stroke can thus be calculated as 1.6 % on the operated side and 0.8 % on the contralateral side in this group of 64 patients. If the 30 patients who died during follow-up are included, the figures appear as 1.2 % and 0.8 % respectively. The differences in stroke rate between the operated and contralateral side are not statistically significant (chi-square). In six patients anticoagulant therapy was given following the recurrent ischemic events.

The results of the vascular (Doppler) follow-up examinations are given in Table 2 a and b. In order to evaluate the incidence of progressive carotid lesions, the Doppler results are related to previous angiographic studies, viz., the post-operative findings on the operated side and the pre-operative findings on the contra-lateral side. The patients with TIA and stroke in each territory during the observation period (see above) are indicated with T and S respectively. Table 2 a shows that, on the operated side, 15/42 patients (36 %) or, if the right column is included 20/58 (36 %) of the patients, had developed post-operative changes (stenosis ≥ 50 % or occlusion). On the

Table 2 b. Vascular (Doppler) follow-up on contralateral, non-operated side related to pre-operative angiographic findings

		Pre-operative angiography		
		plaque/stenosis < 50 %	stenosis ≥ 50 %	occlusion
Follow-up (Doppler):	normal			
	N	31	28	4
	normal*	24 T	18	1
	stenosis (≥ 50 %)	7 S S	10 T	3 S
occlusion		-	-	-
		-	-	1

*for definitions, see text

contra-lateral side (Table 2 b), a progression of lesions was detected in 17/63 patients (27 %). On both sides, the occurrence of new ischemic symptoms was mainly restricted to vessels with progressive changes. However, in 26 out of 37 vessels with disease progression, this was not associated with any clinical symptoms. The incidence of progressive vascular lesions is not significantly different between the operated and contra-lateral, non-operated side (chi-square).

Because surgery was mainly confined to patients with a significant stenosis only on the appropriate side, the evolution of a severe carotid lesion cannot be evaluated from these data. However, a subgroup of 18 patients, in whom pre-operative angiographies showed only plaque/stenosis < 50 % on the operated side, can be compared to 28 patients with similar changes on the contra-lateral side. On the operated side only 2/18 progressive lesions occurred as opposed to 10/28 on the contra-lateral side. Statistical analysis (Fisher's exact test) gives a $p = 0.06$, indicating a more favourable course after endarterectomy than after non-surgical management.

DISCUSSION

The incidence of recurrent stenosis on the operated side, found in the present study, is considerably higher than that previously reported for symptomatic recurrent stenosis. Stoney and String (14) described 29 patients with a symptomatic recurrent lesion, 24 of whom were collected from the authors own series of 1654 carotid operations. French and Rewcastle (8) estimated the recurrence rate to 0.6 % from cases of their own and cases reported in the literature, but they considered this figure to be unrealistically low. Cossman et al (7) reported a recurrence rate of 3.6 % within 24 months after surgery. In a personal inquiry by Callow (6), the overall incidence of recurrent stenosis at various centers was 1.13 % with a range of 0.2 to 4.75 %. The number of operations surveyed was 13 470.

In the present report only 11 out of 37 vessels (29.7 %) with progressive lesions had associated clinical symptoms. The major proportion of the progressive carotid lesions was clinically silent. In total, 28 patients (43.8 %) had developed new lesions in one or both carotid arteries. After endarterectomy, the disease progression on the operated and non-operated side were not significantly different.

Non-invasive methods have previously been used in a few studies to detect the incidence of asymptomatic recurrent stenosis after endarterectomy.

The various results obtained may be explained by differences in methods and times of the follow-up. Kremen et al (10) studied 173 operated carotid arteries with ocular pneumoplethysmography. They found a symptomatic and asymptomatic recurrence rate of 1.7 % and 1.8 % respectively. Maximum time of follow-up was 12 years, however, only 27 of the patients were examined six years or more after the operation. Because oculopneumoplethysmography is an indirect test, only hemodynamically significant stenoses or occlusions may be detected. Turnipseed et al (15) found an asymptomatic recurrence rate of 9 % in 70 patients examined 3 years after surgery. They used Doppler imaging and spectral analysis of carotid flow in the bifurcation region, and compared post-operative and pre-operative findings. However, the precise criteria for a positive finding were not stated. Brodily et al (3) examined 69 carotid arteries at 3 to 96 months after carotid surgery by means of Duplex scan (B-mode imaging and pulsed Doppler). Three different quantitative Doppler criteria, each stated to indicate a stenosis > 50 %, gave a widely variable outcome. 49 % of the examined vessels demonstrated flow abnormalities in at least two of the three Doppler variables. No information is provided on the material of patients studied concerning risk factors, age or treatment during follow-up.

The incidence of progressive arterial disease found in this study is consistent with the natural evolution of carotid bifurcation atheroma, as determined by serial angiographies by Javid et al (9). Of 86 patients, 51 had increased severity of stenosis 1-9 years after the first angiography. In 32 patients (38.9 %) the progression in the degree of stenosis exceeded 25 % per year. Progressive disease was associated with hypertension and initial degree of stenosis. Bauer et al (2) examined 49 patients with repeat angiography after a mean interval of 25 months. Progression of lesions was detected in 17 of 63 carotid arteries (27 %) not operated.

It seems unlikely that technical factors at endarterectomy should be responsible for the high recurrence rate found in this study, because post-operative angiography showed an acceptable result in the vast majority of the vessels. Moreover, early angiographic changes have been seen later to remodel and become smooth (13). However, an unexpected finding was the high frequency of carotid occlusion post-operatively, which was clinically silent in 4 out of 7 patients.

Two different pathological processes have been identified at the site of recurrent stenosis. Myointimal proliferation has been found mostly within 1-2 years after surgery whereas recurrent lesions occurring later have been related to progressive arteriosclerosis (7, 14). The relationship between

the two pathological conditions are at present not entirely known. In the present study, arteriosclerosis seems to be the most likely cause of recurrent lesions, because these were mostly detected late.

The present findings do not seem to negate the probable value of carotid surgery in the group of patients studied. In a selected group of patients with a severe symptomatic carotid stenosis, not associated with major lesions in other vessels, carotid endarterectomy appears reasonable, although unequivocal support is not available from any study that would satisfy all statistical and epidemiological criteria. Incomplete information is presently available on the relationship between the risk of future stroke and degree and type of stenosis. Moore et al (11) found an average annual stroke rate of 0.4 % in asymptomatic patients with minimal ulceration as opposed to 12.5 % in patients with large or compound ulceration. In the Canadian Cooperative Study (1) the value of antiplatelet therapy was disappointing in patients with angiographic evidence of extensive involvement of a large number of cerebral arteries. Recently, Busuttil et al (5) reported that patients with hemodynamically significant stenosis treated non-surgically were at significantly greater risk for cerebrovascular death, stroke and TIA than patients treated operatively. In patients with non-hemodynamically significant stenosis treated medically the risk of cerebrovascular death and stroke was only 2.2 % during a 5 year follow-up

Provided that the present findings are representative, a, mostly clinically silent, progression of carotid lesions in one or both carotid arteries can be expected in almost half of the patients with unilateral carotid endarterectomy. Carotid surgery should not be regarded as definitive treatment, and close follow-up and careful control of riskfactors after surgery is equally important as in patients medically treated for cerebral ischemia.

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CAROTID ARTERY OCCLUSION:

Acute Symptoms and Long-term Prognosis

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ABSTRACT

A material of fifty-nine patients with carotid artery occlusion diagnosed 1968-1977 was studied. The presenting symptoms were ipsilateral TIA in 12 patients, stroke in 41, nine of which died in the acute phase, and TIA-stroke from other vascular territory in 6 patients. 39 % of the patients had preceeding TIA. At the time of follow-up (mean 48 months) only 2 cases with TIA and 2 with stroke on the occluded side were found. Seven patients had recurrent symptoms from other vascular regions. Twelve patients died during follow-up due to diseases unrelated to stroke. Thus, the annual incidence of ipsilateral stroke ($\sim 1\%$) and TIA ($\sim 1\%$) was low. Anticoagulant treatment in 20 of the patients may have contributed to the low recurrence rate.

INTRODUCTION

The surgical procedure of superficial temporal artery-middle cerebral artery (SIA-MCA) bypass operation has been advocated in patients with otherwise inaccessible arterial lesions, and occlusion of the internal carotid artery has been considered as one of the main indications (Sundt et al., 1976, Spetzler 1979). However, despite the obvious technical success of bypass surgery, the appropriate criteria for the selection of the patients have not been established (Whisnant 1978).

Assessment of the prophylactic value of bypass surgery in patients with carotid artery occlusion necessitates comparison with the natural long term prognosis, which has so far not been established, although an extensive joint study is underway (McDowell 1977). In addition, the knowledge of the pathophysiological mechanisms in carotid occlusion is incomplete, e.g. the importance of different patterns of collateral circulation and the relative contribution of hemodynamic and thromboembolic factors in producing ischemic symptoms.

In this paper the initial clinical features and long term prognosis in 59 patients with carotid occlusion will be described. In a following study (Norrving et al. 1981), based on the same material of patients, possible pathophysiological mechanisms of cerebral ischemic events in carotid artery occlusion will be discussed.

MATERIAL AND METHODS

Fifty-nine patients with carotid occlusion treated at the Neurological Department, University Hospital, Lund, Sweden during 1968-1977 and mainly living in the local uptake area form the basis of the present report. Patients with carotid occlusion due to trauma, arteritis or following carotid surgery were not included. In 56 cases the presumed etiology was arteriosclerosis, while in 3 patients late effects of radiation therapy to the neck region was the possible cause.

Clinical records were reviewed. The patients were followed for a mean time of 48 months. At the time of follow-up 1979 the 38 patients than alive were examined clinically. Reliable follow-up data could be obtained on every patient, even on those who died during the follow-up period.

The diagnosis of occlusion was documented angiographically in 54 patients and in 5 patients, who died in the acute phase, at autopsy only. All patients had an extracranial carotid occlusion: in 53 patients occlusion of the internal carotid artery and in 6 patients occlusion of the common carotid artery.

RESULTS

Mean age of the patients at the time of diagnosis of occlusion was 64.8 years and the ratio male/female was 48/11. Arterial hypertension was present in 25 patients (42.4 %). 13 patients had a myocardial infarction prior to the diagnosis of occlusion. 3 patients had received radiation therapy to the neck previously.

Presenting symptoms (=last symptom prior to the diagnosis of occlusion) are given in Table 1, which also shows symptoms prior to the presenting ones. In 53 patients the presenting symptoms were referable to the occluded side. 12 patients had TIA only, while 41 patients had stroke, 9 of which died in the acute phase. 6 patients had TIA or stroke from the contralateral carotid artery or the vertebro-basilar territory only.

In the group of patients with ipsilateral TIA without stroke (N = 12) 9 patients had episodes of transient monocular blindness only, 2 patients had transient hemispherical attacks only, while 1 patient had both transient hemispherical attacks and episodes of transient monocular blindness on separate occasions. 7/12 patients had multiple TIA:s before the diagnosis of occlusion was established.

In the patients with stroke on the occluded side (N = 41) this was preceded by TIA:s in 11 patients (8 patients hemispherical attacks, 3 patients transient monocular blindness), 8 of which had their last TIA within one week prior to the stroke. TIA:s were multiple in 8 of the patients. In addition, 3 patients had experienced previous strokes referable to the occluded side, occurring in 2 patients one year and in one patient 15 years prior to the diagnosis of occlusion. Angiographic examinations were not performed on these occasions.

The onset of the ipsilateral stroke was sudden in 19 patients, evenly

Table 1. Presenting symptoms (=last symptom before the diagnosis of carotid artery occlusion was established) and symptoms prior to presenting symptoms

Presenting symptom	N	Symptoms prior to presenting symptoms			
		Ipsilateral		Other territory	
		TIA	Stroke	TIA	Stroke
Ipsilateral:					
TIA	12	7		1	2
Stroke	32	9	3	1	
Stroke + *	9	2		1	1
Other territory:					
TIA	2				
Stroke	4				
Total	59	18	3	3	3

* Death mainly due to acute stroke

progressive in 5 and stepwise progressive in 17 patients.

The severity of the presenting ipsilateral stroke in the patients who survived the acute phase was evaluated 3 weeks after the onset of the symptoms. At that time 14 patients had slight residual symptoms while 18 patients had moderate-severe residua. A substantial recovery later than 3 weeks was seen in 8 patients, in 3 of which complete remission of the symptoms occurred.

Of the 9 patients who died in the acute stage 5 died within the first week and the other 4 within the first month. Autopsy was performed in all these patients and in 8 cases revealed a massive hemispherical infarction with transtentorial hernation. One patient had a large infarction but died of pulmonary embolism.

Six patients had no ischemic symptoms referrable to the occluded side. 2 patients had TIA only (1 contralateral carotid, 1 vertebro-basilar) and 4 patients had stroke (2 contralateral carotid, 2 vertebro-basilar).

In total 23 patients had experienced ipsilateral TIA:s, in 16 patients occurring only within the last 2 months before the diagnosis of occlusion was established. It is recognized that the incidence of previous TIA:s might be underestimated due to inability to provide an accurate history in some patients with severe stroke or aphasia.

Follow-up results are given in Table 2. During follow-up (mean 48 months)

Table 2. Recurrent ischemic events during the follow-up period of mean 48 months after the diagnosis of carotid occlusion

Presenting symptoms	N	Recurrent ischemic events			
		Ipsilateral		Other territory	
		TIA	Stroke	TIA	Stroke
Ipsilateral:					
TIA	12	1	1	-	1
Stroke	32	1	1*	3	1*
(Stroke +	9)				
Other territory:					
TIA	2	-	-	-	1
Stroke	4	-	-	1	-
Total	59	2	2	4	3

* Same patient

only two patients had new episodes of TIA and two patients new strokes re-ferrable to the occluded side, representing an average annual incidence of recurrent TIA or stroke of 2 %. One patient had 4-5 ipsilateral TIA:s 6-8 months after diagnosis of occlusion while one patient had multiple hemispherical TIA:s during 6 months after the diagnosis was established. In both patients TIA:s ceased spontaneously. The strokes occurred 1 month and 6 years after diagnosis of occlusion. One patient had a RIND (Reversible Ischemic Neurological Deficit) while the other patient had a stroke with moderate residual symptoms.

TIA or stroke from other territories than the occluded side occurred in 4 and 3 patients respectively and could generally be attributed to arterial lesions in the responsible vessels.

Of the 50 patients who survived the acute phase, 12 patients died during follow-up. The causes of death were: myocardial infarction 4, malignancy 3, gastro-intestinal hemorrhage 2, hepatic cirrhosis, pulmonary embolism and gangrene 1 each. No death was due to recurrent stroke.

Long term anticoagulant treatment (more than 6 months) was given to 20 patients, mainly those with TIA or minor stroke and arteriosclerotic lesions in other vessels also. The recurrence of stroke symptoms related to therapy is given in Table 3.

Table 3. Recurrent ischemic events related to therapy

Therapy	N	Recurrent ischemic events				Total
		Ipsilateral		Other territory		
		TIA	Stroke	TIA	Stroke	
Anticoagulant	20	–	1*	1	1*	3
No therapy	30	2	1	3	2	8

* Same patient

DISCUSSION

The acute effects of carotid occlusion are highly variable and a certain proportion developes carotid occlusion with no clinical abnormality. In an unselected autopsy material carotid occlusion was found in 5.2 % and was associated with clinical symptoms in 79 % (Torvik and Jörgensen 1964, Torvik and Jörgensen 1966). When symptoms occur, these range from TIA to massive hemispheric infarction. Because a carotid occlusion is generally diagnosed by angiography, this induces some selection of the patients presenting with stroke symptoms. Angiography was more commonly performed, with the aim of carotid surgery, in younger patients with slight or no residual symptoms than in older patients with stroke. Thus, clinical materials are unlikely to represent the true incidence and the true clinical spectrum of presentation of carotid occlusion.

In the present material altogether 89.8 % of the patients had symptoms from the territory of the occluded carotid artery. 39 % of the patients had preceeding ipsilateral TIA:s which most commonly occurred only during a short time before the diagnosis of occlusion was established.

When the long term prognosis of new ischemic events is considered, distinction has to be made between symptoms occurring in the distribution of the occluded vessel and symptoms remote from this side. Information on this is not available in any studies (Hurwitz et al. 1959, Hardy et al. 1962, Dyken et al. 1974, Marshall 1966). The total recurrence rate in these studies varies from 2 recurrent stroke among 43 survivors followed for 2.7 years (Hurwitz et al. 1959) to 28 new strokes among 121 survivors in 3.7 years (Hardy et al. 1962). Also, the frequency of new strokes on the occluded side reported in the literature are at some variation. The Joint Study of Extra-

cranial Arterial Occlusion (Fields and Lemak 1976) provides the largest number of patients studied. Of the 359 patients who survived the initial stroke, 35 patients had an ipsilateral stroke during 44 months. However, a further 34 patients had a new stroke where the side was not known. It is not stated how many patients that were treated with anticoagulants. In contrast, Grillo and Patterson (1975) recorded no recurrent stroke on the occluded side in 44 patients followed during 3 years. In the study by Anderson et al. (1977) consisting of 28 patients with an operated contralateral stenosis also no patient had a new ipsilateral stroke during 19 months. There is also variation on reported mortality of the presenting stroke, ranging from 2.9 % (Fields and Lemak, 1976) to 15.9 % (Grillo and Patterson 1975). As stated above, the diagnostic procedure of angiography involves a selection of patients, and the differences reported in the literature probably reflects selection differences.

In the present study only 2 patients had a new stroke on the occluded side during 48 months of follow-up, representing an annual average incidence of only ~1 %. This figure is in agreement with a recent study from the Mayo Clinic (Furlan and Whisnant 1979) where less than 2 % per year of the patients suffered an ipsilateral stroke during follow-up. Thus, the critical period for acquisition of an ischemic deficit is prior to or at the time of occlusion, while after the diagnosis of carotid artery occlusion has been established the frequency of new ischemic events is very low.

The 20 patients who were treated with anticoagulants had a lower incidence of recurrent symptoms irrespective of side than the group of 30 patients where no such therapy was given. However, the small number of patients in these non-randomized groups and the general low recurrence rate precludes further evaluation.

In many studies, including the present, recurrent stroke from other territories than the occluded side equals or exceeds the frequency on the side of occlusion, corresponding to the high incidence of contralateral carotid and vertebro-basilar artery lesions seen in patients with carotid artery occlusion (Fields and Lemak 1976, Norrving et al. 1980).

There is a general agreement of the high incidence of cardiovascular death in patients with carotid artery occlusion, common to that seen in patients with TIA or stroke in general. Cardiac deaths usually outweighs the deaths from recurrent stroke during follow-up.

Bypass surgery can be expected primarily to reduce the frequency of recurrent events on the occluded side only. Taking the present finding of a very low frequency of recurrent stroke on the side of occlusion as repre-

sentative of the true natural course, the value of bypass surgery as a general prophylactic measure in these patients should be questioned. Further studies of the acute and long term course including analysis of the importance of collateral hemodynamics and thromboembolic mechanisms are highly warranted.

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CEREBRAL ISCHEMIC SYMPTOMS IN CAROTID ARTERY OCCLUSION:
Role of hemodynamic factors

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ABSTRACT

In 59 patients with carotid artery occlusion the acute outcome was studied and related to the angiographic pattern of collateral flow. No patient with TIA only had retrograde ophthalmic artery flow, while such a pattern was found in 50 % of the patients with stroke. In a follow-up study (mean 48 months) the same distribution of collateral pattern was found on ultrasonic Doppler examination. Absence of substantial retrograde ophthalmic flow was associated with an increased contralateral carotid flow. The findings show that the efficiency of the collateral pathways, mainly that of the contralateral carotid artery and the circle of Willis, largely determine the outcome of carotid artery occlusion.

INTRODUCTION

The cerebral circulatory system is provided with several collateral pathways which are essential for the adjustment of blood flow to the brain in the event of major vessel stenosis or occlusion. In carotid artery occlusion a large number of alternative pathways has been documented (Fields et al. 1965) but the main collaterals replacing internal carotid flow in occlusive disease are the vertebral and contralateral internal carotid systems via the posterior and anterior communicating arteries of the circle of Willis, and the external carotid artery via retrograde flow in the ophthalmic artery.

Possible mechanisms inducing ischemic symptoms in patients with carotid occlusion includes continuous propagation of the thrombus above the circle of Willis and embolic occlusion in the vascular tree distal to the occlusion as postulated from autopsy studies (Castaigne et al. 1970, Torvik and Jörgensen 1966). Other possible mechanisms involve non-embolic infarction or aggravation of the effects of embolism due to insufficient collateral supply (Fischer 1951). The relative contribution of these factors is, however, unknown, and few studies have been attempted to determine the relative importance of main collaterals. An analysis of these different, pathophysiological mechanisms is of obvious importance for a rational therapeutic and prophylactic approach, including the selection of patients for arterial bypass surgery.

In the present study a clinical material of patients with carotid artery occlusion has been analyzed in order to relate the cerebral ischemic symptoms to hemodynamic factors as evaluated by means of angiography and ultrasonic Doppler examination.

MATERIAL AND METHODS

The study is based on a material of 59 patients with the diagnosis of carotid artery occlusion examined at the Department of Neurology, University Hospital, Lund during the period 1968 to 1977, and reexamined 1979.

A. Clinical symptoms

The patients were primarily grouped according to the presenting clinical symptoms and signs (see Results). A detailed account of these acute (and the long-term) clinical events is given in an accompanying study (Norrving and Nilsson, 1981).

B. Angiography (and autopsy)

The diagnosis was established by angiography in 54 patients, while 5 patients, all of which died in the acute phase, were examined only at autopsy. Angiography was performed in 13 patients within the first week, in 28 patients in week 2-4 and in 13 within 1 to 8 months after the manifestation of the presenting symptoms. Aortic arch angiography was performed in 29 patients and selective carotid angiography on the occluded side in 35. In addition, contralateral selective carotid angiography was performed in 6 patients.

The initial angiographic examinations were reviewed in detail (S.C.) to determine the site of occlusion, collateral flow via the circle of Willis and via the ophthalmic artery, presence of intracranial arterial lesions distal to the occlusion and the occurrence of arterial lesions in extracranial arteries other than the occluded carotid artery. Based on these examinations, collateral flow via the ophthalmic artery was designed as RR when filling of the entire territory of the middle cerebral artery (MCA) was seen, R when only part of the MCA territory or the carotid siphon only was seen, and 0 when no retrograde ophthalmic flow was visible. Ophthalmic flow was possible to evaluate mainly in patients in which selective ipsilateral carotid angiographies had been performed and in some additional cases from aortic arch angiographies. Cross filling via the circle of Willis was evaluated on aortic arch angiographies or contralateral carotid angiographies, and was designed as significant when filling of the entire territory of the MCA on the occluded side was seen.

C. Ultrasonic Doppler examination

All 38 patients alive at the time of follow-up 1979 were examined with Ultrasonic Doppler technique (Parks Continuous Wave Directional Doppler Model 906). All patients were examined in a standardized procedure in the supine position after 10 minutes rest. The common, internal and external carotid, the ophthalmic and vertebral arteries were examined (von Reutern et al. 1976, Büdingen et al. 1976). Vertebral arteries were examined with an emitted Doppler frequency of 5.3 MHz while the other vessels were examined at 9.7 MHz. Velocity curves, recorded on a kymograph (Elema-Schönander, Solna,

Sweden) were obtained from each patent vessel. The carotid arteries were examined along their extracranial course for signs of stenosis or occlusion (von Reutern et al. 1976).

Flow in the contralateral carotid arteries was quantified from the end diastolic value of the Doppler velocity curve (Risberg and Smith 1979, Mahler et al. 1977). Since more than half of the patients had a contralateral internal carotid stenosis, invalidating measurements at this site, the common carotid artery was used for the determinations of the contralateral flow. Care was taken not to include the carotid bifurcation region in the recording. The Doppler probe was positioned in approximately 45° angle to the common carotid artery. With this setting, a 1 KHz Doppler frequency shift represents a velocity of 10.93 cm/s, as also determined from calibration experiments at known velocities. Signs of stenosis in the contralateral common carotid artery were not seen neither in patients examined with Doppler nor in the group initially examined with angiography. The flow velocity values were compared with the corresponding values obtained in an age matched group of 96 patients with transient symptoms not attributed to carotid TIA (isolated vertigo, diplopia, transient amnesia, brief episodes of loss of consciousness) and without signs of carotid stenosis on Doppler examination, or with TIA within the carotid territory but without signs of stenosis on angiographic examination (Norrving, unpublished data).

Ophthalmic artery flow was designed as 0 when ortograde flow or zero flow was seen on Doppler examination. Retrograde flow was designed as R or RR. These two categories were found to be bimodally distributed both when maximal systolic velocity (Kaneda et al. 1979) and the end diastolic velocity were used as index. To allow comparison with the results of Kaneda et al. (1979) maximal systolic velocity was used, R denoting values below -2 KHz (slight retrograde ophthalmic flow) and RR denoting retrograde flow exceeding -2 KHz (substantial retrograde ophthalmic flow).

Since vertebral recordings in our experience are more difficult to evaluate than carotid recordings, these were not subjected to quantitative analysis in the present study.

RESULTS

A. Clinical symptoms

As shown in the accompanying study dealing with clinical characteristics of the material of 59 patients (Norrving and Nilsson 1980), 12 had TIA

without infarction on the side of carotid occlusion, and 41 had a stroke on this side, 9 of which died in the acute phase. Of the surviving stroke patients 14 had slight residual symptoms (minor stroke) and 18 had moderate to severe residua (major stroke) when evaluated 3 weeks after the onset of symptoms. Six patients had TIA or stroke only from other territories than the occluded side.

B. Angiography and autopsy findings

1. Contralateral carotid artery. The carotid artery contralateral to the occluded side was examined with angiography or at autopsy in 40 patients, 22 of which were found to have a contralateral carotid stenosis of 50 % or more.

2. Ophthalmic artery. Ophthalmic artery flow could be angiographically evaluated in 39 patients (Table 1). It can be seen in the table that a substantial retrograde ophthalmic flow was found mainly in patients with major stroke. Patients with ipsilateral TIA only or vascular symptoms from other territories had no retrograde ophthalmic flow.

3. Intracranial arteries. The patients with ipsilateral TIA or symptoms unrelated to the side of occlusion all had evidence of adequate MCA filling via the circle of Willis, mainly via the anterior communicating artery (ACA). Thirty-two patients with stroke on the occluded side survived the acute phase. In 11 of these, examined with ipsilateral carotid angiography only and with no or slight retrograde ophthalmic flow, it was not possible to evaluate the intracranial vessels distal to the occlusion. However, in two patients filling of the carotid siphon could be seen, and one patient who died during follow-up was examined with autopsy which did not reveal any intracerebral occlusion. In 15 patients with ipsilateral stroke the intracerebral vessels distal to the occlusion were clearly visible and showed no evidence of arterial luminal defects. Occlusion of the main stem of the MCA (physically separated from the extracranial carotid occlusion) was seen in 4 patients (1 with minor stroke, 3 with major stroke), while peripheral branch occlusion of the MCA was seen in 2 patients (both with major stroke).

4. Autopsy findings. The 9 patients who died in the acute phase all had a massive hemispheric infarction, herniation being the possible cause of death in 8. One patient died of pulmonary embolism. In 4 patients continuous propagation of the thrombus to the MCA was seen while another 4 patients had an anomalous circle of Willis with aplasia of the ACA and no evidence of intracerebral vessel occlusion. In one patient the protocol of the intracranial vessel examination was incomplete.

Table 1. Presenting clinical symptoms and ophthalmic artery flow as determined from angiographic examinations in 39 patients

Presenting symptoms	N	Ophthalmic flow		
		O	R	RR
<u>Ipsilateral:</u>				
TIA	8	8	-	-
Stroke: Minor	13	8	4	1
Major	15	6	4	5
Other territory:	3	3	-	-

Table 2. Ophthalmic artery flow (Doppler examination) in 32 follow-up patients related to presenting clinical symptoms

Presenting symptoms	N	Ophthalmic flow		
		O	R	RR
<u>Ipsilateral:</u>				
TIA	9	8	1	-
Stroke: Minor	9	6	3	-
Major	10	2	3	5
Other territory:	4	2	1	1

C. Doppler findings

At the time of follow-up 38 patients were examined with Doppler.

1. Carotid artery flow. In 3 patients the Doppler examination indicated a bilateral carotid occlusion. This could have been present initially in 2 patients since the contralateral carotid artery was not angiographically examined. In 3 patients the findings were consistent with recanalisation of the occlusion. One of these patients had an ipsilateral stroke during follow-up.

2. Ophthalmic and contralateral carotid artery flow. The Doppler findings of ophthalmic artery flow in the remaining 32 patients with persistent unilateral carotid occlusion is given in Table 2. As in Table 1 it is seen that patients presenting with TIA or minor stroke on the occluded side or no symptoms referable to this side generally had no or only slight retrograde ophthalmic artery flow. A substantial retrograde ophthalmic flow was again mainly seen in patients who had suffered a major stroke. Fig 1 gives the flow velocity in the contralateral common carotid artery related to the ophthalmic flow (individual data). In the figure the mean values from the "control" group is indicated for comparison. Patients with no (0) or only slight retrograde ophthalmic flow (R) had contralateral flow values above the mean "control" values, while patients with a substantial retrograde flow (RR) had no contralateral flow increase. In Figure 2 contralateral carotid flow velocity is expressed as per cent of the age-matched control value and related to the different ophthalmic flow patterns. Patients with no or slight retrograde ophthalmic flow had a contralateral flow of $162 \% \pm 4.6$ (S.E.M.) and $143 \% \pm 7.6$ respectively, whereas patients with a substantial retrograde flow had no contralateral flow increase ($89.2 \% \pm 11.1$). The difference in contralateral carotid flow between patients with no (0) or slightly retrograde (R) ophthalmic flow and patients with substantial retrograde ophthalmic flow (RR) is highly significant ($p < 0.001$, Student's t-test), whereas the difference between patients with no and slight retrograde flow is not significant.

D. Angiographic vs. Doppler findings

The material permitted a direct comparison between the results of the initial angiographic findings and the follow-up Doppler findings in 36 patients. As reported above (C:1) one patient had a Doppler finding indicating a newly developed contralateral carotid occlusion, while in 3 patients recanalisation of the occluded artery was found. A change in ophthalmic artery flow was seen in one patient with ipsilateral TIA and in 2 patients with stroke symptoms from other territories than the occluded side. These 3 pa-

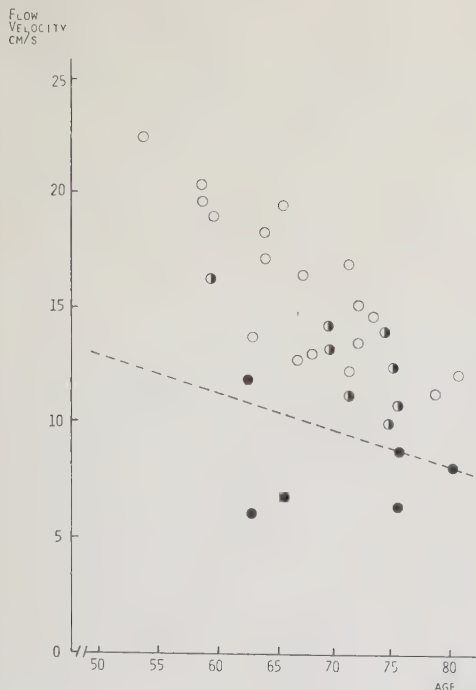


Figure 1. Flow velocity in the contralateral common carotid artery in 38 patients at the time of follow-up. Broken line indicates mean values of "control" group (see text). ○ denotes patients with orthograde or zero ophthalmic flow, ◐ slightly retrograde and ● substantial retrograde ophthalmic artery flow.

CONTRALATERAL
CAROTID FLOW
(MEAN $\pm$ S.E.M.)

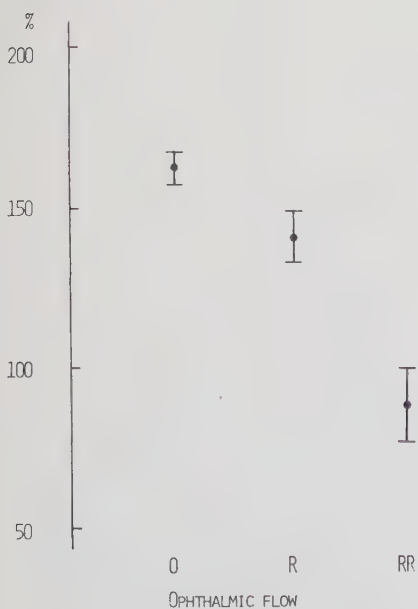


Figure 2. Contralateral carotid flow (per cent of corresponding "control" value) related to pattern of ophthalmic artery flow.

tients had no retrograde ophthalmic flow initially while Doppler examination showed a slight retrograde flow (R) in two patients and a substantial retrograde flow (RR) in one patient. In the remaining cases no anatomical or hemodynamic differences were found.

DISCUSSION

As shown in the accompanying clinical study (Norrving and Nilsson, 1980) the patients of the present material showed highly varying, often recurrent, ischemic symptoms in the period immediately preceeding the establishment of the diagnosis of carotid artery occlusion, while, during follow-up, very few new ischemic events occurred. Although the selection of patients should to some extent favour such a distribution of symptoms, it is reasonable to conclude that the cerebral ischemic symptoms are related in time to the development of severe vessel stenosis finally leading to occlusion.

The present study emphasizes the importance of hemodynamic factors in determining the acute effects of a carotid artery occlusion. The collateral circulation via the circle of Willis and via retrograde flow in ophthalmic artery constitute the two major collateral pathways in patients with carotid artery occlusion, provided intracranial propagation of the thrombus has not occurred. In the latter case more distal and less efficient collateral systems, mainly leptomeningeal anastomoses come into play (Nilsson et al. 1979). Both the initial angiographic and the follow-up Doppler-findings demonstrate that the vast majority of patients without ipsilateral ischemic symptoms, or with ipsilateral TIA only, have efficient collateral flow from the contralateral carotid system via the ACA. In contrast, about half of the patients developing a permanent ischemic deficit had retrograde ophthalmic flow, and the findings of a substantial retrograde ophthalmic flow was usually associated with a severe deficit. The pattern of a marked retrograde ophthalmic flow was correlated to absence of contralateral carotid flow increase, again showing the primary importance of the contralateral carotid-ACA capacity.

The results corroborate the findings of Pitts (1962) and Fogelholm and Vuolio (1969), who showed that patients with retrograde ophthalmic flow generally had more severe deficits, although obviously sufficient collateral supply via the ophthalmic artery has been documented in some clinical studies (Contee and Vijanathan 1979, Fields et al 1961). In addition to angiography, the Doppler technique provides a useful method for the functional assessment of the collateral circulation into the brain. In the present study, the

findings of a contralateral flow increase of 62 % and 43 % in patients with no or slight retrograde ophthalmic flow respectively, would indicate adequate circle of Willis function in both instances, whereas patients with a substantial retrograde ophthalmic flow had no contralateral flow increase. The direction and magnitude of the ophthalmic flow thus mirrors the collateral flow via the circle of Willis. This is in accordance with the Doppler results recently published by Hodek-Demarin and Müller (1979). The values of contralateral carotid flow can be compared with those found utilizing electromagnetic flow meters. Nornes (1973) studying patients considered for a carotid ligation for carotid aneurysms, stated that a contralateral flow increase in excess of 40-50 % would indicate a sufficient collateral supply via the circle of Willis. Symon et al. (1963) found that occlusion of one carotid artery in the baboon produced an immediate increase in blood flow through the opposite carotid artery of 42.5 ± 10 %.

The collateral capacity of the circle of Willis depends on the anatomical features of the circle but in patients with cerebrovascular disease also on the contralateral internal carotid, and the vertebro-basilar arteries. Thus, in the present material about half of the patients can be estimated to have substantial contralateral carotid stenosis. In autopsy studies circle of Willis anomalies have been found in 27 % (Fawcett and Blackford 1963) to 81 % (Riggs and Rupp 1963), some of which should however not interfere with the collateral capacity. Most commonly anomalies of the posterior communicating arteries have been found. In patients with a normal circle of Willis the potential of rapid flow adjustment has been documented (Symon et al. 1963, Stern 1962), while the calibre and length of the ophthalmic artery probably precludes its rapid development to a high capacity collateral channel.

It should be pointed out that, in addition to the hemodynamic mechanisms analyzed in the present study, emboli and possibly propagation of a thrombus from the internal carotid artery are common complications of carotid disease. Although difficult to assess quantitatively, embolism alone or in combination with collateral insufficiency may well be the cause of cerebral ischemia in many of our patients. The autopsy findings in 8 patients with large infarctions, 4 having MCA occlusion and 4 ACA aplasia, clearly illustrate these two mechanisms. Further, the large proportion of patients with a carotid artery occlusion having preceeding, in most cases multiple TIAs which appear to cease when carotid occlusion has been established, suggests embolic mechanisms. Patients in which the vascular tree distal to a carotid occlusion or tight stenosis is visualized by angiography in the acute phase have a high frequency of intracranial vessel occlusion. In a study by Einsiedel-Lechtape

(1979) 33/37 patients (= 89 %) with ipsilateral stroke and carotid occlusion had evidence of intracerebral luminal defects representing embolism. Pessin et al. (1979) found embolism or suspected embolism in 42/64 patients (= 66 %). Also in autopsy studies intracerebral embolism is frequently seen: 40/63 patients (= 63 %) in the study of carotid occlusion by Castaigne et al. (1970). Early angiographic examination may be essential in documenting all instances of embolism because lysis may occur within a short time after the embolic episode (Dalal et al. 1965).

In conclusion, the study shows that the acute outcome of carotid artery occlusion is largely determined by hemodynamic factors, the capacity of the circle of Willis being the main determinant, and the occurrence of a retrograde ophthalmic flow being a sign of insufficient collaterals. Embolic mechanisms or propagation of thrombus appear to be equally important. The combined effects of embolism and low perfusion should also be taken into account. The autopsy findings of the present series clearly illustrate the two mechanisms discussed: 4 cases having aplasia of the ACA and 4 MCA occlusion.

Relatively few new ischemic events occurred during follow-up despite the finding in some patients of a flow pattern indicating insufficient collaterals. This does not exclude the possibility that in the chronic state some patients with carotid artery occlusion suffer from low or borderline cerebral hemisphere perfusion. These patients should benefit from flow augmenting operations, since hemodynamically this state may currently impair cerebral function or aggravate a "permanent" deficit (Nilsson et al. 1979) but probably also increase cerebral vulnerability to new embolic events. Although at present the exact indications for shunt procedure have not been adequately defined (Whisnant 1978), patients considered for operation should be strictly evaluated with regard to the total collateral situation. This evaluation should then include analysis of clinical state, angiography, ultrasonic Doppler examination, and preferably, regional blood flow studies.

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rCBF IN PATIENTS WITH CAROTID OCCLUSION: Resting and hypercapnic flow
related to collateral pattern

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SUMMARY

rCBF was measured by ^{133}Xe inhalation technique in 39 patients with unilateral carotid artery occlusion in a subacute-chronic stage. Resting flow values (ISI) varied between 23.7 and 52.4 ml/100 g/min. An almost constant finding was interhemispheric asymmetry, the degree of which was correlated with the severity of the initial symptoms. Ischemic focus was an insignificant finding. The CO_2 response was normal in patients with angiographic signs of circle of Willis collateral flow and without significant contralateral carotid stenosis, whereas it was impaired in patients with a retrograde ophthalmic flow or collateral flow via the circle of Willis and contralateral carotid stenosis $\geq 50\%$. It is concluded that the CO_2 response is a useful rCBF variable and may be applied for analysis of collateral flow capacity in patients with carotid artery occlusion considered for bypass surgery.

INTRODUCTION

Carotid occlusion is the single most common arterial lesion considered for extra-intracranial bypass operation.¹ Although this procedure is performed in numerous patients, its definitive therapeutic value remains unproven. In most centers, bypass surgery is confined to patients with TIA or only mild stroke at the time of the occlusion, and is attempted to reduce the incidence of future stroke.

Recent studies suggest that the long term prognosis in carotid occlusion is favourable, with a stroke rate on the occluded side of only 1-2 % per year.^{2,3} This would limit the value of bypass surgery as a general prophylactic measure in carotid occlusion. Because a bypass operation is a hemodynamically directed procedure, the identification of a subset of patients with impaired capacity of the collateral circulation would be of importance.

In this report we examine the usefulness of rCBF (regional Cerebral Blood Flow) studies in evaluating hemodynamic features in carotid occlusion. rCBF was measured with the ¹³³Xenon-inhalation technique during rest and induced hypercapnia and results were correlated with clinical symptoms and collateral flow pattern.

MATERIAL AND METHODS

The material consists of 39 patients with unilateral carotid occlusion examined with rCBF by ¹³³Xenon inhalation. The patients were collected in the following manner. 26 patients were evaluated for bypass operation after angiographic identification of the occlusion at this or at an admitting hospital. The interval between the onset of the symptoms and the rCBF study was one to six months in these patients. From a recent study on the long-term prognosis in carotid occlusion³ a further 13 patients with previous TIA or minor stroke were randomly selected for rCBF examination, performed one to nine years after the diagnosis of occlusion was established. The

ratio male/female was 31/8 and the mean age of the patients was 60 years (range 34-77 years).

Angiograms were examined for presence of lesions in extracranial arteries other than the occluded carotid as well as intracranially, and for source of collateral supply to the occluded hemisphere. All patients underwent selective common carotid angiography on the occluded side. The contralateral carotid artery was studied with selective angiography in 33 patients and with aortic arch angiography in 6 patients. The vertebral arteries, examined in 30 patients, were studied selectively in 10 patients and with aortic arch angiography in 20 patients. The intracranial vessels distal to the internal carotid occlusion were clearly visualized in each patient. No patient had extension of the carotid thrombus beyond the circle of Willis nor major arterial lesions within the territory of the middle cerebral artery (MCA).

Source of collateral supply to the occluded hemisphere was designated as "ophthalmic" or "Willisii" type. These two pathways constitute the major collaterals in carotid occlusion.⁴ In patients with collateral flow of the "ophthalmic" type, the entire territory of the MCA on the occluded side was filled via this route with no or virtually no filling via the circle of Willis. In patients with the "Willisii" type, cross-filling via the anterior or posterior communicating arteries filled the entire MCA territory on the occluded side, but in some patients a slight retrograde ophthalmic flow was also present. However, via the latter route only the carotid siphon or a small part of the proximal MCA territory were visualized. In 22 out of 24 patients with collateral flow via the circle of Willis, the anterior communicating artery was the main supplying vessel.

CT-scan was performed in 27 patients, in 26 later than one week after the onset of the symptoms. Infarctions visualized were classified as lagunar (localized to the internal capsule, adjacent lentiform nucleus or corona radiata and less than 2 cm in diameter), small superficial (less than 3 cm in diameter) and large (major part of the MCA territory).

rCBF measurements were made by the ¹³³Xenon-inhalation technique as described by Obrist et al.⁵ The present ¹³³Xenon-inhalation system (Novo Diagnostic Systems, Inhalation Cerebrograph, Denmark) enables simultaneous measurement of cerebral blood flow in 16 homologous regions of both hemispheres by 32 scintillation detectors (3/4" x 3/4" NaI (Tl) crystals; lead collimators 20 mm deep and 22.5 mm wide) placed at right angle to the lateral surfaces of the head. ¹³³Xenon mixed with air (90 MBq/l) was inhaled by the patients for one minute through a tight-fitting mask and a rebreathing

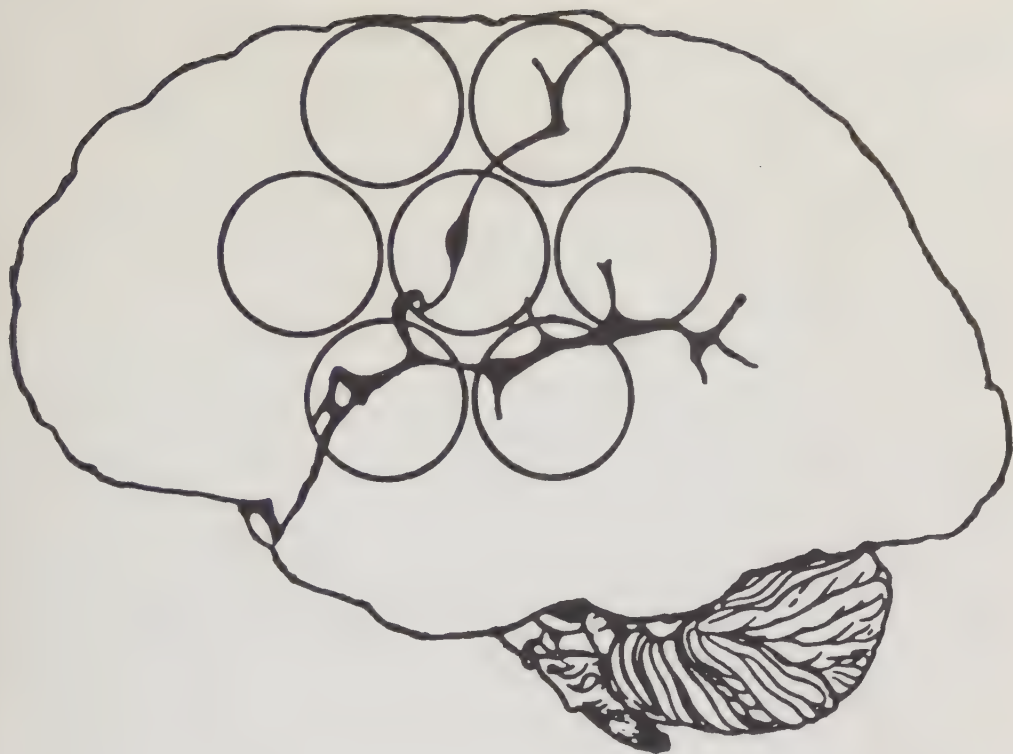


Fig. 1. Assumed average location of the 7 detectors related to the cortex.

spirometer system. This period was followed by 10 minutes of normal breathing. Arterial $p\text{CO}_2$ was estimated from recordings of end-tidal CO_2 concentrations (Beckman LB 2 CO_2 -analyzer). For a detailed technical description of the present ^{133}Xe inhalation technique, see Risberg 1980⁶ and Risberg & Prohovnik 1981⁷.

Because the main region of interest in patients with carotid occlusion is the territory of the MCA, only the rCBF values from the seven detectors overlying the distribution of this vessel were used in this study. Detector localization is depicted in Figure 1. Of the different rCBF variables, obtained by computer analysis, the ISI (Initial Slope Index) was utilized in this study because it is the most reliable variable in conditions with low flow and unstable compartments.^{7,8} The ISI is calculated from the slope of the head curve (corrected for recirculation) from 1 to 2 minutes following the end of the ^{133}Xe breathing.

The distribution of the rCBF values within the seven detectors over the MCA territory was evaluated for presence of ischemic focus. A focus was de-

fined from the inter-regional distribution as a region with a rCBF value less than -2.0 S.D. of the distribution seen in normal subjects.⁹

Twenty patients had a consecutive rCBF measurement during inhalation of 4 % (6 patients) or 6 % (14 patients) of CO₂ mixed with air, causing a mean increase in arterial pCO₂ of 11.0 mmHg (range 6.8-15.7 mmHg). The CO₂-air mixture was inhaled for 5 minutes prior to the ¹³³Xenon inhalation, discontinued for technical reasons during the one minute isotope intake and recommended for an additional 10 minutes.

There is no uniformity of opinion on the shape of the CBF/p_aCO₂ relationship within the physiological range (25-60 mmHg). An exponential relationship has been found by some authors¹⁰ while others have reported a linear response.^{11,12} For the results in this study, calculation of the CO₂ response as ml CBF/ mmHg p_aCO₂ or log ml CBF/ mmHg p_aCO₂ yielded the same separation into normal and impaired responses. Therefore, CO₂ is expressed only as ml CBF/ mmHg p_aCO₂ in the text. During CO₂ administration a slight increase in blood pressure (less than 10 mmHg) was recorded in most patients.

RESULTS

We divided the 39 patients into three groups according to the initial clinical symptoms. In Group I (N = 14) ten patients had TIA only and one patients retinal stroke on the occluded side, whereas an asymptomatic occlusion had been detected in three patients examined for contralateral TIA. Group II (N = 18) consists of patients with a cerebral infarction with no or only mild residual symptoms, whereas Group III (N = 7) includes patients with cerebral infarction and moderate or severe residua. Cerebral infarctions in Group II and III were restricted only to the distribution of the occluded carotid artery in all patients but one. This patient had a RIND (Reversible Ischemic Neurological Deficit) from the contralateral carotid territory one year prior to a severe ipsilateral stroke.

Table 1 details the angiographic findings. A stenosis ≥ 50 % in the contralateral carotid artery was seen in nine patients and in one or both vertebral arteries in five patients. In Group I collateral flow was mainly of the "Willisii" type, whereas in Group III the "ophthalmic" type prevailed. In Group II, the two patterns were more evenly distributed. Of the (in total) nine patients with a contralateral carotid stenosis > 50 %, four had collateral flow of the "Willisii" and five of the "ophthalmic" type.

CT was performed in seven patients in Group I; it was normal in five and revealed a small lacunar infarct in two patients, one of whom had an asymptomatic occlusion and one patient TIA clinically. In Group II, CT-scan, performed in 14 out of the 18 patients, showed: small superficial infarction 6, lacunar infarction 5 and a normal finding 3 patients. In Group III CT-scan visualized a large infarction in all seven patients.

The rCBF results (mean of seven detectors) during rest are given in Figures 2-4 (individual data) and Table 2 (mean values). Mean rCBF values on the occluded side were slightly lower in Group II than in Group I (n.s.), whereas patients in Group III had markedly reduced rCBF values on both the occluded and the non-occluded side (Table 2). All but two patients had lower rCBF values on the side of the occlusion (Figures 2-4). The inter-hemispheric rCBF asymmetries were more pronounced in Group II than in Group I, and still greater in Group III, intergroup differences being highly significant ($p < 0.01$, Wilcoxon's test). The rCBF values or side asymmetries did not correlate with the time interval between the initial symptoms and the rCBF examination, nor was there any association with the collateral pattern seen in Group I or II.

rCBF examination was repeated in five patients in Group I and II after an interval of 6-12 months from the first study, which had been performed within 6 months after the onset of the symptoms. In three patients a slight decrease in rCBF was found (1-3 ml/100 g/min). However, two patients (both in Group II) had markedly higher rCBF on the second study without concomitant change in $p_2\text{CO}_2$. rCBF values had increased from 30.9 and 36.6 to 44.7 and 41.3 ml/100 g/min respectively. Both patients had been treated conservatively.

An ischemic focus within the seven detectors was found in 11 patients. Two patients had two regions with focally decreased flow whereas nine patients had only one detected focus. The appearance of a focus did not correlate with the time interval between the initial symptoms and the rCBF study or with the collateral pattern, nor with the CT finding of an infarction.

The CO_2 response was determined in 20 patients in Group I and II (Figure 5). The CO_2 reactivity was expressed as change in ml CBF per mmHg change in $p_a\text{CO}_2$. The normal value of 0.75 ml/mmHg $p_a\text{CO}_2$ found in normal subjects¹³ is indicated in the figure. A clear relationship between the type of collateral pattern and the CO_2 reactivity on the occluded side is seen ($p < 0.001$, chi-square). Seven out of eight patients with collateral flow of the "ophthalmic" type had impaired CO_2 response on the occluded side, in addition to three patients with the "Willisii" type of collateral flow

Fig. 2-4. rCBF results during rest in Group I-III. Symbols indicate type of collateral flow:

	Group		
	I	II	III
Type of collateral flow: Willisii	$\triangle$	$\square$	$\circ$
Willisii + ctr	$\triangle$	$\square$	$\circ$
Stenosis $\geq 50\%$	$\triangle$	$\square$	$\circ$
Ophthalmic	$\triangle$	$\square$	$\bullet$

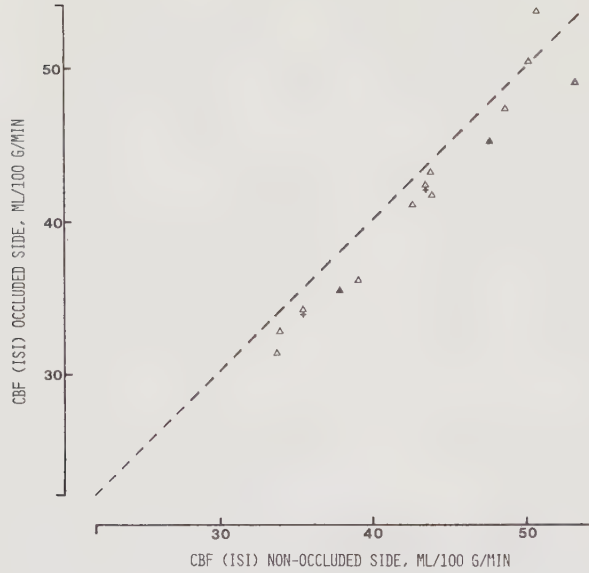


Fig. 2.

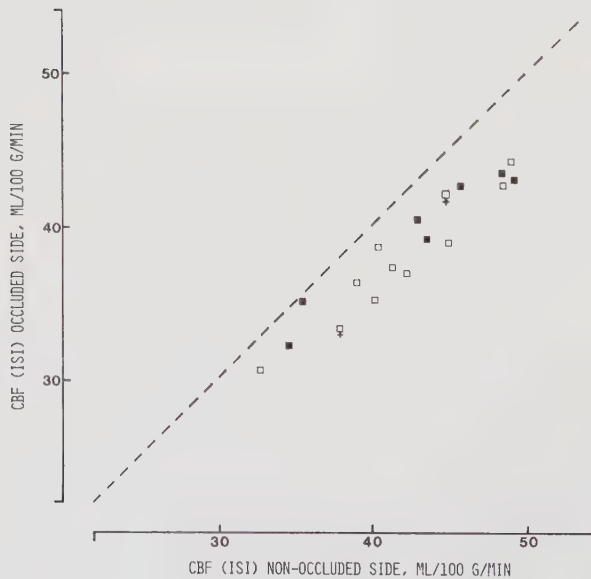


Fig. 3

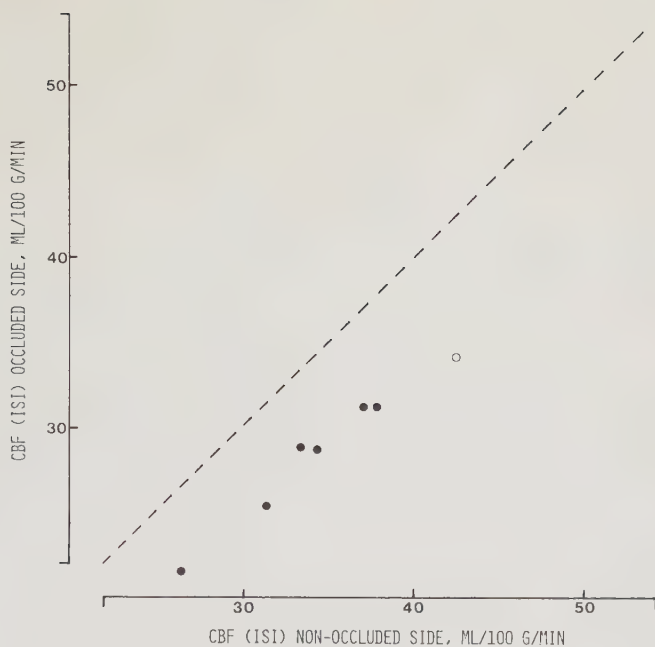


Fig. 4

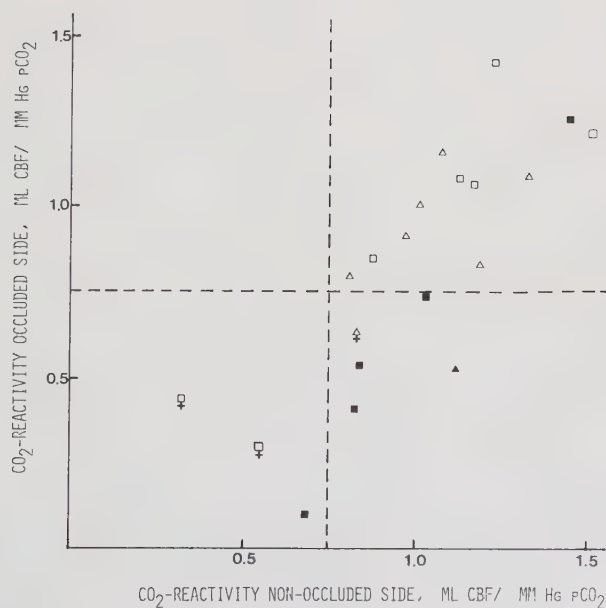


Fig. 5. rCBF response to induced hypercapnia. Symbols, see Fig. 2-3.

Table 1. Mean age, angiographic findings and type of collateral flow in the different groups of patients

Group	N	Mean age	Contralateral carotid artery normal/stenosis < 50 %	stenosis $\geq$ 50 %	Vertebral arteries		Type of collateral flow	
					Normal	Stenosis $\geq$ 50 %	unknown	Willisii
I	14	63.1	12	2	13	1	-	12
II	18	57.9	13	5	12	3	3	11
III	7	56.6	5	2	-	1	6	1
								6

Table 2. rCBF results

Group	N	Time interval < 6 months	init. > 1 year	sym - rCBF	rCBF, ISI (mean of 7 detectors)		CBF, occluded - contralateral side	N of patients with ischemic focus
					occluded side	contralateral side		
I	14	7	7		41.9	42.9	- 1.0 xx	4
II	18	14	4		38.7	42.2	- 3.5 xx	5
III	7	7	-		29.2	34.9	- 5.7	2

xx = $p < 0.01$ (Wilcoxon's test)

and concomitant significant stenosis in the contralateral carotid artery. Conversely, all 10 patients with collateral flow via the circle of Willis, not associated with significant stenosis in the contralateral carotid artery, had a normal CO₂ response. The time interval from the initial symptoms to the rCBF study did not seem to interfere with the CO₂ response. Nine patients were examined later than one year after the diagnosis of occlusion had been established, four of whom had decreased CO₂ reactivity. Also, no association between the resting rCBF values and the CO₂ response was found.

The CO₂ response was largely homogeneous within the seven detectors studied, including the five patients with ischemic focus and seven patients in Group II with an infarct visualized by CT-scan. A CO₂ response deviating > 20 % of the mean reactivity was seen only in five patients in one or at most two of the detectors. No region with non-reactivity or paradoxal response was seen.

DISCUSSION

Cerebral blood flow studies have previously been performed to determine the value of this technique in selecting patients for bypass surgery. Using the intracarotid technique, Schmiedek et al.¹⁴ stated that patients with an ischemic focus in association with no or only moderate general rCBF reduction were the most suitable candidates for surgery. Similar conclusions were reached by Heilbrun et al.¹⁵ However, the intracarotid technique encounters specific problems in patients with obstructive lesions, which must be considered in the interpretation of data.¹⁶ The contribution of different vessels, chosen for isotope injection, to the blood flow of the occluded hemisphere is variable. If collateral flow is poor, an adequate delivery of isotope to the occluded hemisphere may be critical. Also, if isotope is injected in the contralateral carotid artery, radiation from the non-occluded hemisphere will contaminate the recording on the occluded side to a variable extent. The use of ¹³³Xenon inhalation, and also the intravenous ¹³³Xenon technique,¹⁷ partly circumvents the problem of isotope delivery encountered in patients with carotid occlusion. Moreover, its non-invasiveness facilitates sequential studies with time and during various conditions.

In this study, three types of rCBF data were specifically analyzed, viz., the resting rCBF values, the presence of an ischemic focus and the CO₂ response.

As compared to age-matched controls,¹⁸ subnormal rCBF values on the

occluded side were found in about two thirds of the patients with TIA or asymptomatic occlusion and in all patients with minor stroke. In patients with a severe stroke rCBF was more markedly reduced on both sides. Although "cross-talk" tends to underestimate true side differences in blood flow,¹⁹ an inter-hemispheric asymmetry was generally observed. The inter-hemispheric rCBF differences mainly paralleled the clinical state of the patients.

The spontaneous return of an initially subnormal rCBF to the normal range was observed in two patients, not subjected to surgery. This implies that the finding of an increased rCBF after a bypass procedure has to be cautiously interpreted, unless rCBF studies are performed close to the time of the operation.

The definition of an ischemic focus must take into account the normal hyperfrontal distribution of the rCBF. Normally, parietal regions have a rCBF 4-7 % below the hemispheric mean.⁹ In this study, an ischemic focus, defined from the normal intra-hemispheric distribution, was found to be present in less than one third of the patients. However, it must be emphasized that with conventional external scintillation detectors the regionality of the method is limited. Scattered radiation (Compton scatter) tends to suppress regional differences in rCBF, and because the detector system views the tissue as a truncated cone, heterogeneous tissue elements are superimposed.^{20,21} Also, the wash-out method by its very nature does not permit recognition of areas of absent or very poor perfusion. An adequate amount of isotope may not reach the area of focal ischemia, in which case radiation originating in deeper or adjacent tissues will dominate the clearance curves. Thus, the importance of focus detection, as a selection criterion for bypass surgery, seems to be limited from methodological reasons.

The finding of a subnormal mean rCBF or an ischemic focus does not necessarily imply that the blood flow into the region is restricted by the capacity of the collateral circulation or the intracerebral vessels. In this study, also patients with a low resting rCBF could increase flow substantially during induced hypercapnia. We believe that a subnormal rCBF mainly reflects an adaptation to the reduced demands of the tissue. If so, a bypass procedure would not necessarily be of benefit. A more precise definition of the indications of therapy intended to increase the cerebral blood flow would require the relationship between the metabolic demands by the tissue and the available blood flow to be determined. In most stable stroke patients, rCBF and the metabolic rate have been found to be proportionally depressed.²² However, data by Crubb et al.²³ show that this relationship may be deranged also in the chronic state. Presently, regional measurements

of metabolic rate can only be obtained by positron emission tomography, the costs and practical aspects of which limit its broad use.

The third type of rCBF data analyzed in this report, the rCBF response to induced hypercapnia, was found to be the most informative.

Of various tests, performed with the attempt to study the cerebrovascular reserve in occlusive disease, CO₂ administration has the advantage of exerting only vascular effects. The induction of hypertension by norepinephrine is associated with a usually mild hyperventilatory response. More important, norepinephrine may have specific metabolic effects on the cerebral parenchyma, which are more pronounced when the blood-brain barrier is disrupted.²⁴ The rCBF response to various physiological activation procedures is mediated via the parenchyma, the state of which will be critical for the full effect of the activation. Besides, normally the rCBF response to activation procedures is considerably less pronounced than to hypercapnia.¹³

An abnormal CO₂ reactivity in stroke patients is mainly seen in the acute phase, and if no major arterial occlusion is present, the CO₂ response is usually later regained.²⁵ In patients with only TIA or minor stroke and without major vessel pathology, a normal CO₂ response in the chronic phase has been found.²⁶ In the present study, a decreased CO₂ reactivity was found in only three of the patients with the CT finding of an infarction, two of which were lacunar. In the corresponding rCBF areas, as well as in regions with an ischemic focus, the CO₂ response paralleled the mean response of the seven detectors studied. Therefore, a reduced CO₂ response, as found in this study in some patients in Group I and II, will have to be attributed to the specific hemodynamic factors present.

In a previous study on pathophysiological mechanisms in the acute phase of carotid occlusion,⁴ the circle of Willis was found to be the most efficient collateral pathway, whereas a collateral supply via the ophthalmic artery was associated with more severe stroke symptoms. This study reveals a similar relationship between these two collateral pathways and the ability to increase blood flow during induced hypercapnia. In addition to patients with retrograde ophthalmic flow, patients with a collateral supply via the circle of Willis associated with a contralateral carotid stenosis $\geq 50\%$ were found to have an impaired CO₂ response.

Considering collateral flow via the ophthalmic artery, the diameter of this vessel is about equal to a normal, patent anterior communicating artery.^{27,28} However, the considerable length of the former collateral route probably is critical for its function as a full capacity collateral able to

increase flow substantially.²⁹

The hemodynamic importance of even a moderate stenosis in the carotid artery contralateral to an occlusion is often not fully recognized. During normal conditions a carotid stenosis is of hemodynamic significance only when the cross-sectional area is reduced to about 80 % or more.^{30,31} However, in patients with a carotid occlusion and collateral flow via the circle of Willis, flow in the contralateral carotid artery has been found to be increased about 40-60 %.^{4,32} Since the pressure drop across a stenosis is strongly dependent on the flow rate through the vessel, stenoses also of lesser degree are hemodynamically significant when flow is increased.^{29,33} When a contralateral carotid artery serves both hemispheres, stenoses of about 65-70 % reduction in cross-sectional area, corresponding to about 40-55 % decrease in diameter, will be critical.³³

In patients with an impaired CO₂ response, a reduced peripheral resistance, i.e. a vasodilatation of intracerebral arterioles on an autoregulatory basis, may be present already in the resting condition. The contribution of this latter factor to the reduced CO₂ response is not specifically answered by this study because the autoregulatory response to hypotension was not tested. However, the finding of low perfusion pressures (down to 9-15 mmHg) in the middle cerebral artery or a cortical artery during intra-operative measurements in a proportion of patients with chronic carotid occlusion^{34,35} makes it reasonable to assume that in some patients the autoregulatory reserve may be diminished, making these patients susceptible to cerebral ischemia during transient drops in blood pressure due to decreased cardiac output or postural hypotension. While an induced hypotension test would be of interest in patients with carotid occlusion, the practical aspects of its safe execution limit its use.

Evaluation of the possible prophylactic benefit of bypass surgery must take into account the pathophysiological mechanisms of post-occlusion ischemic events. These may be caused both by hemodynamic factors and by embolism. A transient drop in blood pressure due to decreased cardiac output or postural hypotension is often assumed as a cause, but has been clearly documented in only few patients.^{36,37,38} However, due to its transient state, a drop in perfusion pressure may easily escape detection. It has recently been shown that post-occlusion ischemic events may also be of embolic origin. Possible sources of emboli are the "proximal" stump^{38,39} and distal "tail"⁴⁰ of the occluded carotid artery, arterial lesions in the external carotid artery^{41,42} or other collateral pathways and concomitant intracranial lesions distal to the occlusion. In patients where the mechanism of ischemia

is related to emboli, the possible benefit of a bypass would be a redistribution of flow in collateral pathways with an embolic source, or to an increase in the tolerance of a marginally perfused region to withstand emboli without the development of infarction.¹⁷

The present finding, that a majority of the patients with carotid occlusion and no or only minor stroke have an adequate reserve capacity of the collateral circulation, should imply that a bypass operation in these patients is not required from a hemodynamic point of view. The finding of an impaired CO₂ response does not provide full information about the adequacy of the collateral circulation to the occluded hemisphere in the resting condition, but identifies a subset of patients in whom further studies may reveal a possible role of bypass surgery. It also remains to be investigated whether a bypass is a more efficient collateral than the ophthalmic artery or simply would redistribute flow from the latter vessel.⁴³ In patients with collateral flow via the circle of Willis associated with a significant contralateral carotid stenosis, an endarterectomy of the stenosis would be the procedure of choice also from a hemodynamic point of view, provided that this operation can be performed with sufficiently low morbidity.^{44,45,46,47}

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